



**Protocol Title**

A phase II trial of concurrent chemoradiation with consolidation Pembrolizumab for the treatment of inoperable or unresectable stage III non-small cell lung cancer (NSCLC):  
LUN14-179

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**Trial Management Provided by**

Hoosier Cancer Research Network, Inc. (HCRN)

Funding Support and Pembrolizumab Provided By  
Merck Sharp & Dohme Corp. ("Merck")

**Investigational New Drug (IND) Application ID#: 125073**

**Initial Protocol Date:** 08JAN2015

**Amended Protocol Version Date:**

08JAN2015

09JUL2015

26SEP2015

14JAN2016 (current)

## PROTOCOL SIGNATURE PAGE

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LUN14-179

### **VERSION DATE: 14JAN2016**

I confirm I have read this protocol, I understand it, and I will work according to this protocol and to the ethical principles stated in the latest version of the Declaration of Helsinki, the applicable guidelines for good clinical practices, or the applicable laws and regulations of the country of the study site for which I am responsible, whichever provides the greater protection of the individual. I will accept the monitor's overseeing of the study. I will promptly submit the protocol to applicable ethical review board(s).

Instructions to the investigator: Please **SIGN** and **DATE** this signature page. **PRINT** your name and title, the name and location of the facility in which the study will be conducted, and the expected IRB approval date. Scan and email the completed form to Hoosier Cancer Research Network and keep a record for your files.

\_\_\_\_\_  
Signature of Investigator

\_\_\_\_\_  
Date

\_\_\_\_\_  
Investigator Name (printed)

\_\_\_\_\_  
Investigator Title

\_\_\_\_\_  
Name of Facility

\_\_\_\_\_  
Location of Facility (City and State)

\_\_\_\_\_  
Expected IRB Approval Date

☐ Not Submitting to IRB

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## SYNOPSIS

<b>TITLE</b>	A phase II trial of concurrent chemoradiation with consolidation pembrolizumab for the treatment of inoperable or unresectable stage III non-small cell lung cancer (NSCLC)
<b>SHORT TITLE</b>	Consolidation pembrolizumab following chemoradiation in subjects with inoperable/unresectable stage III NSCLC
<b>PHASE</b>	Phase II
<b>OBJECTIVES</b>	<p><u>Primary Objective:</u> To determine if consolidation therapy with pembrolizumab following concurrent chemoradiation improves time to death or distant metastatic disease, depending on which occurs first, in subjects with inoperable or unresectable stage IIIA or IIIB NSCLC. Distant metastasis is defined as anything that is outside of the radiation field.</p> <p><u>Secondary Objectives:</u></p> <ul style="list-style-type: none"> <li>• To determine if consolidation therapy with pembrolizumab following concurrent chemoradiation improves progression free survival (PFS) and overall survival (OS) in subjects with inoperable or unresectable stage IIIA or IIIB NSCLC.</li> <li>• To assess toxicity and tolerability of consolidation therapy with pembrolizumab following concurrent chemoradiation in subjects with inoperable or unresectable stage IIIA or IIIB NSCLC.</li> <li>• Time To Death in evaluable set</li> </ul> <p><u>Exploratory Objectives:</u> To assess PD-L1 expression levels in the tumor samples of subjects with inoperable or unresectable stage IIIA or IIIB NSCLC and correlate with time to distant metastatic disease, tumor histology, PFS, OS, and treatment toxicity.</p>
<b>STUDY DESIGN</b>	This is an open label, multi-institutional, single arm phase II trial of consolidation therapy with pembrolizumab following initial treatment with concurrent chemoradiation in subjects with inoperable or unresectable stage IIIA or IIIB NSCLC. No randomization or blinding is involved.
<b>ESTIMATED NUMBER OF SUBJECTS</b>	N = 93

<p><b>ELIGIBILITY CRITERIA</b></p>	<p><b><u>Inclusion Criteria:</u></b></p> <ol style="list-style-type: none"> <li>1. Written informed consent and HIPAA authorization for release of personal health information.</li> <li>2. Age <math>\geq</math> 18 years at the time of consent.</li> <li>3. Histological or cytological evidence of NSCLC.</li> <li>4. Must have unresectable or inoperable stage IIIA or IIIB disease. Subjects are considered unresectable or inoperable based on the judgment of the treating physician.</li> <li>5. Subjects may have completed concurrent chemoradiation with a standard chemotherapy regimen (Cisplatin/Etoposide, Carboplatin/Paclitaxel or Cisplatin/Pemetrexed) and a dose of radiation ranging from 59.4-66.6 Gy. Subjects must have stable disease or disease response as evidenced on CT or PET scan evaluation. For those eligible, pembrolizumab should begin a minimum of 28 days and a maximum 56 days following the completion of chemoradiation. <b>OR</b></li> <li>6. Subjects may have completed up to 2 cycles of consolidation therapy started within 4 weeks of completion of radiation. After completion of consolidation therapy, subjects must have stable disease or disease response as evidenced by CT or PET scan evaluation. For those eligible, pembrolizumab should begin 3-4 weeks after the last cycle of chemotherapy.</li> <li>7. Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1 within 14 days prior to registration for protocol therapy.</li> <li>8. Adequate laboratory values obtained within 14 days prior to registration for protocol therapy (see protocol for details)</li> <li>9. Women of childbearing potential must be willing to use two methods of contraception or abstain from heterosexual activity from the point of registration through 120 days after the last dose of study drug.</li> <li>10. Male subjects of childbearing potential must agree to use an adequate method of contraception starting with the first dose of the study drug and through 120 days after the last dose of the study drug.</li> </ol> <p><b><u>Exclusion Criteria:</u></b></p> <ol style="list-style-type: none"> <li>11. Pregnant or breastfeeding, or expecting to conceive or father children within the projected duration of the trial, starting with the pre-screening or screening visit through 120 days after the last dose of trial treatment.</li> <li>12. Active central nervous system (CNS) metastases. Subjects must undergo a head computed tomography (CT) scan or brain MRI within 28 days prior to registration for protocol therapy to exclude brain metastases if symptomatic or without prior brain imaging.</li> <li>13. Treatment with any investigational agent within 28 days prior to registration for protocol therapy</li> <li>14. Prior chemotherapy, adjuvant therapy, or radiotherapy for lung cancer other than standard concurrent chemoradiation or up to 2 cycles of consolidation as described above</li> </ol>
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	<ol style="list-style-type: none"> <li>15. Prior therapy with a PD-1, PD-L1, PD-L2 or CTLA-4 inhibitor or a lung cancer-specific vaccine therapy</li> <li>16. Presence of metastatic disease (stage IV NSCLC) is not allowed. Subjects must be evaluated with a PET scan prior to registration for protocol therapy to exclude metastatic disease.</li> <li>17. Active second cancers.</li> <li>18. Active autoimmune disease requiring systemic treatment within the past 90 days or a documented history of clinically severe autoimmune disease, or a syndrome that requires systemic steroids or immunosuppressive agents. Subjects with vitiligo or resolved childhood asthma/atopy would be an exception to this rule. Subjects that require intermittent use of bronchodilators or local steroid injections would not be excluded from the study. Subjects with hypothyroidism stable on hormone replacement or Sjogren's syndrome will not be excluded from the study</li> <li>19. Presence of interstitial lung disease or history of pneumonitis requiring treatment with corticosteroids</li> <li>20. Diagnosis of immunodeficiency or receiving chronic systemic corticosteroid therapy or other immunosuppressive therapy (excludes inhaled corticosteroids) within 7 days of first dose of study drug</li> <li>21. History of psychiatric illness or social situations that would limit compliance with study requirements.</li> <li>22. Clinically active infection as judged by the site investigator (<math>\geq</math> Grade 2 by CTCAE v4).</li> <li>23. History of human immunodeficiency virus (HIV) infection or chronic hepatitis B or C.</li> <li>24. History or current evidence of any condition, therapy, or laboratory abnormality that might confound the results of the trial, interfere with the subject's participation for the full duration of the trial, or is not in the best interest of the subject to participate, in the opinion of the site investigator.</li> <li>25. Has a known history of active TB (Bacillus Tuberculosis).</li> <li>26. Hypersensitivity to pembrolizumab or any of its excipients.</li> <li>27. Has received a live vaccine within 30 days prior to planned start of study therapy.</li> </ol> <p><b>NOTE:</b> Seasonal influenza vaccines for injection are generally inactivated flu vaccines and are allowed; however intranasal influenza vaccines (e.g., Flu-Mist®) are live attenuated vaccines, and are not allowed.</p>
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<p><b>STATISTICAL CONSIDERATIONS</b></p>	<p><b>Criteria for stopping the study</b> After the 10th subject is treated with at least one dose of study drug and observed for a minimum of 90 days after first dose of study therapy, further accrual will be halted to evaluate “unacceptable toxicities warranting early closure of the trial” defined as a) any definitive pembrolizumab-related death; or b) any unexpected and previously unreported grade 4 toxicities definitely related to pembrolizumab. If such events are observed in one subject, the DSMB will discuss and provide recommendations to the sponsor-investigator whether to terminate the trial. If such events are observed in two or more subjects, the trial will be terminated.</p> <p>Evidence for pembrolizumab-related death will be continuously monitored through the trial.</p> <p>Pneumonitis of grade 3 and 4 will be continuously monitored. An overall rate of 20% or above would be considered unacceptable. If the probability of the grade 3/4 pneumonitis rate being less than 20% drops below 0.1, the trial will be terminated.</p> <p><b>Sample size, Accrual, Study Duration and Replacement Rules</b> Efficacy of pembrolizumab will be quantified and evaluated by the time to death or distant metastasis, depending on which occurs first. Under the conventional chemotherapy, the median time is around 12-months. We expect pembrolizumab to improve the median time by 50%. Brookmeyer and Crowley method will be used to test the following one-sided hypotheses: <math>H_0: m \leq 12\text{-month}</math> versus <math>H_a: m &gt; 12\text{-month}</math>. The accrual period is expected to be 24-months, following by an additional 12-months follow-up. Thus, the overall study duration will be 36 months. With type I error level as 0.05, <math>N=83</math> subjects are required to obtain a power level of 0.80. The sample size is further adjusted to <math>N = 93</math> to account for 10% lost-to-follow-up. If an ineligible subject is accidentally enrolled, that subject will be removed and replaced with an eligible subject.</p> <p><b>Primary Objective Analysis</b> The primary objective is to evaluate the time to death or distant metastasis (TTD), depending on which occurs first. The enrolled set will be used for the primary analysis.</p> <p>Kaplan-Meier method will be used for estimation. Brookmeyer and Crowley method will be used to calculate the 95% confidence interval of the median time and to test the following one-sided hypotheses: <math>H_0: m \leq 12\text{-month}</math> versus <math>H_a: m &gt; 12\text{-month}</math>. P-value <math>&lt; 0.05</math> will be considered as significant.</p>
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	<p><b>Secondary Objectives Analysis</b> Key secondary objectives are progression free survival (PFS), overall survival (OS) and toxicities of pembrolizumab TTD in evaluable set is also a secondary objective.</p> <p>PFS and OS will be estimated by Kaplan-Meier method. They will be analyzed for both the enrolled set and the evaluable set. TTD will be estimated by Kaplan-Meier method for the evaluable set. Toxicities will be presented as rates and 95% Agresti-Coull confidence intervals. The treated set will be used for toxicity analysis.</p> <p><b>Safety Analysis</b> The Common Terminology Criteria for Adverse Events (CTCAE) v4 and the Merck criteria for immunological side effects will be used jointly to report toxicities.</p> <p>Safety analyses will be performed for the treated set. Toxicities will be summarized by grade level, with and without considering relevance to treatment.</p> <p><b>Exploratory Objective Analysis</b> Exploratory analysis is planned to characterize the rate of expression PD-L1 in stage III NSCLC, and correlate with histology, PFS, OS and toxicity. Rates and 95% confidence intervals will be generated for PD-L1 expressions. Their associations with TTD, PFS and OS will be evaluated by Cox proportional hazard models.</p> <p><b>Subgroup Analysis</b> Both efficacy and toxicity outcomes will be evaluated in subgroup analysis based on PD-L1 expressions, as well for subjects that have had up to 2 cycles of consolidation therapy. Additional subgroup analyses will be performed for toxicities based on primary treatment as chemotherapy or radiation therapy, and the dosage of radiations.</p>
<b>ESTIMATED ENROLLMENT PERIOD</b>	Estimated months = 24
<b>ESTIMATED STUDY DURATION</b>	Estimated months = 36

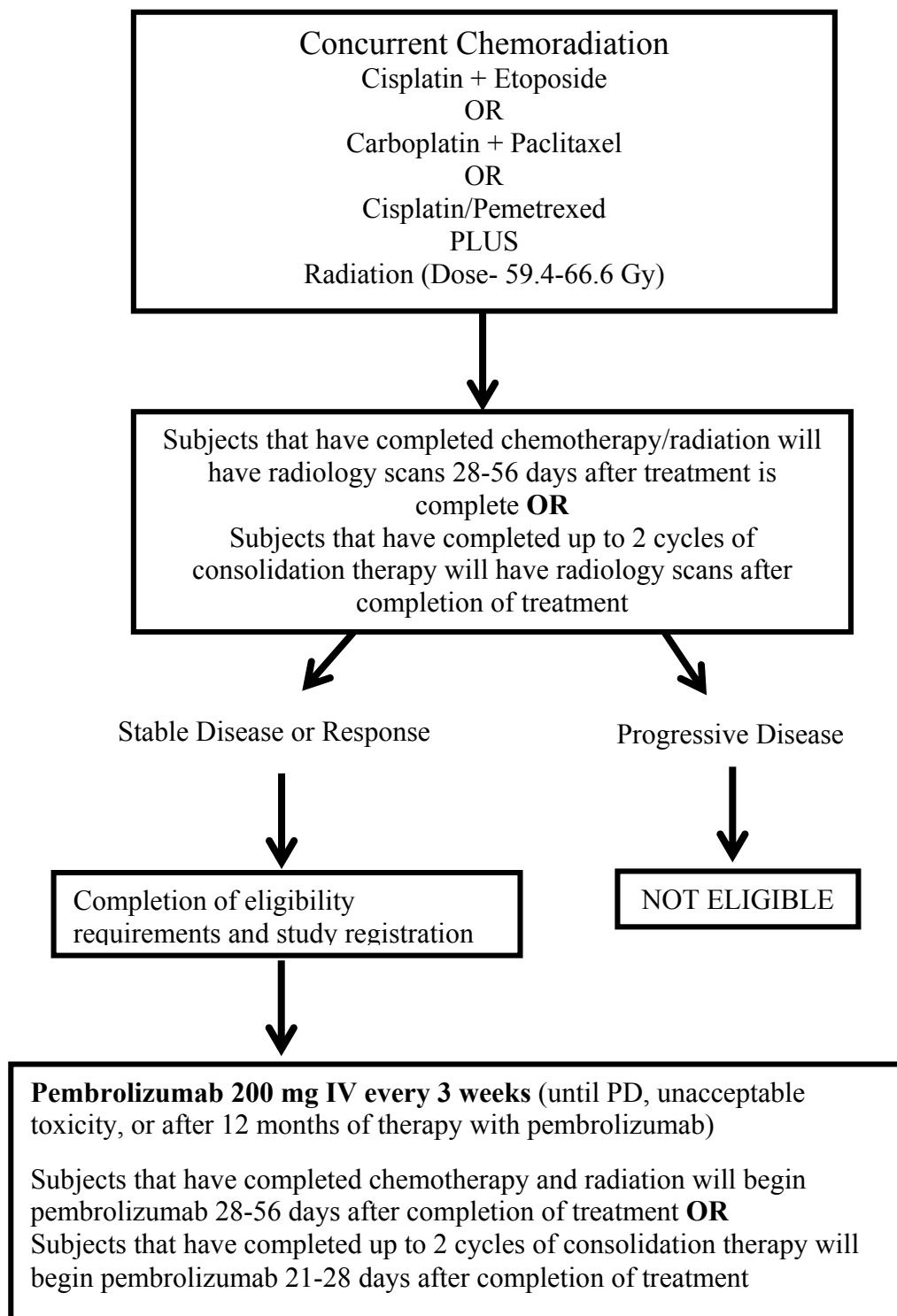
## TABLE OF CONTENTS

<b>SCHEMA</b> .....	9
<b>1. BACKGROUND AND RATIONALE</b> .....	10
<b>2. STUDY OBJECTIVES</b> .....	14
<b>3. ELIGIBILITY CRITERIA</b> .....	14
<b>4. SUBJECT REGISTRATION</b> .....	17
<b>5. TREATMENT PLAN</b> .....	17
<b>6. TREATMENT DISCONTINUATION</b> .....	28
<b>7. STUDY SCHEDULE OF EVENTS</b> .....	30
<b>8. CRITERIA FOR DISEASE EVALUATION</b> .....	33
<b>9. BIOLOGICAL SPECIMEN PARAMETERS FOR CORRELATIVES</b> .....	40
<b>10. STUDY DRUG INFORMATION</b> .....	40
<b>11. ADVERSE EVENTS</b> .....	41
<b>12. STATISTICAL CONSIDERATIONS</b> .....	46
<b>13. TRIAL MANAGEMENT</b> .....	49
<b>14. DATA HANDLING AND RECORD KEEPING</b> .....	49
<b>15. ETHICS</b> .....	51
<b>16. REFERENCES</b> .....	53



## SCHEMA

A phase II trial of concurrent chemoradiation with consolidation pembrolizumab for the treatment of inoperable or unresectable stage III non-small cell lung cancer (NSCLC)



## **1. BACKGROUND AND RATIONALE**

### **1.1 Background**

Refer to the Investigator's Brochure (IB)/approved labeling for detailed background information on Pembrolizumab.

#### **1.1.1 General Background**

Lung cancer is currently the leading cause of cancer-related mortality in the United States and in the world. It is estimated that 159,260 patients will die of lung cancer in 2014, accounting for 27% of all cancer deaths. It accounts for more deaths than breast, prostate, and colorectal cancer combined [1, 2]. Non-small cell lung cancer (NSCLC) accounts for approximately 85% of all primary lung malignancies [3]. Outcomes for this disease are poor, with the five-year OS rate for NSCLC being only 16.8%. This is due largely to the fact that only a small minority of patients (15%) have localized disease at the time of diagnosis [2]. Furthermore, with the exception of molecularly targeted agents in metastatic disease, current therapies for advanced NSCLC provide only modest benefits, and new approaches are needed to improve future outcomes in this disease.

Stage IIIA/IIIB NSCLC is one area with a specific need for new therapeutic modalities, particularly in those patients with unresectable or inoperable tumors. The five-year survival rate for patients with stage IIIA and IIIB NSCLC are 14% and 5%, respectively [4]. The landscape of treatment for these patients has not changed considerably in the last three decades, and the improvements that have been made are relatively limited. Until the 1980s, radiotherapy alone was the standard of care for patients with locally or regionally advanced NSCLC, despite five-year survival rates of only 3-10% [5]. Therefore, two separate trials were done, from Cancer and Leukemia Group B (CALGB) and the Intergroup cooperative trial, which demonstrated that chemotherapy followed by sequential radiotherapy improved five-year OS [5, 6]. Future studies focused on the comparison between sequential and concurrent chemoradiation, and these trials showed a modest improvement in OS for concurrent treatment [7, 8]. This finding was confirmed in a meta-analysis showing an absolute benefit of 4.5% at five years, favoring concurrent chemoradiation over sequential chemoradiation [9]. Since that time, a number of therapeutic strategies have been tried including induction [10, 11], consolidation [11-15], and maintenance chemotherapy [16], but none of these approaches has demonstrated a significant improvement in OS.

Recent trials involving immunotherapeutic targeting of T-cell regulation and activation have demonstrated encouraging results. Ipilimumab, an antibody against cytotoxic T-lymphocyte antigen-4 (CTLA-4), was one of the first therapies developed to target regulatory T-cell function and has demonstrated improved progression free survival (PFS) in a phase II trial of advanced NSCLC [17]. More recently, therapies targeting an alternate T-cell regulatory protein, programmed death-1 (PD-1), have shown very favorable results in early-phase trials. Like CTLA-4, PD-1 is a negative regulator of T-cell function, and new therapies are aimed at blocking this pathway to allow increased T-cell anti-tumor activity. Previous studies have shown that tumor samples demonstrating higher numbers of tumor-infiltrating lymphocytes (TIL) are associated with longer OS [18]. Thus, it would seem logical that therapies directed toward activating the T-cell mediated antitumor immune response might also prolong

survival. One of the first PD-1 inhibitors, Nivolumab, has shown both single-agent activity [19] and activity in combination with a platinum doublet [20] in early-phase trials of patients with NSCLC. Pembrolizumab is also demonstrating encouraging results in phase I trials, including an expanded cohort of patients with advanced NSCLC. Patients treated with single-agent pembrolizumab exhibited an objective response rate (ORR) of 24% based on immune-related response criteria (irRC) and 21% using the response evaluation criteria in solid tumors (RECIST) 1.1. Furthermore, as of the time of the first analysis, seven of the nine responding patients by irRC remain on therapy [21]. Based on these promising results, future trials with therapies that target T-cell regulation and activation are certainly warranted.

A recent abstract presented at the American Society of Clinical Oncology's (ASCO) annual meeting in 2013 suggests that patients with stage III NSCLC may benefit from immune-based therapies. This study randomized 1513 patients to receive either L-BLP25 (Tecemotide), a mucin-1 (MUC1) antigen specific cancer vaccine, or placebo following initial treatment with chemoradiation for unresectable or inoperable stage III NSCLC. Approximately 65% of patients received concurrent chemoradiation, and 35% received sequential chemoradiation. Only 1239 patients were analyzed because of an FDA hold on further treatment with this medication during the initial treatment course in 274 patients. The study failed to meet its primary endpoint of improved OS, but a pre-planned subgroup analysis showed an improvement in median OS from 20.6 months to 30.8 months ( $p=0.016$ ) in those patients treated with concurrent chemoradiation [22]. These findings in combination with the encouraging results from CTLA-4 and PD-1 inhibitors suggest that NSCLC may be more sensitive to immunoregulatory therapies than previous thought. Based on this, we propose a multi-institutional, single-arm phase II trial of consolidation therapy with PD-1 inhibitor pembrolizumab following initial treatment with concurrent chemoradiation in patients with unresectable or inoperable stage IIIA or IIIB NSCLC.

### **1.1.2 Pharmaceutical and Therapeutic Background**

The importance of intact immune surveillance in controlling outgrowth of neoplastic transformation has been known for decades [23]. Accumulating evidence shows a correlation between tumor-infiltrating lymphocytes (TILs) in cancer tissue and favorable prognosis in various malignancies [24-28]. In particular, the presence of CD8<sup>+</sup> T-cells and the ratio of CD8<sup>+</sup> effector T-cells / FoxP3<sup>+</sup> regulatory T-cells seems to correlate with improved prognosis and long-term survival in many solid tumors.

The PD-1 receptor-ligand interaction is a major pathway hijacked by tumors to suppress immune control. The normal function of PD-1, expressed on the cell surface of activated T-cells under healthy conditions, is to down-modulate unwanted or excessive immune responses, including autoimmune reactions. PD-1 (encoded by the gene *Pdcd1*) is an Ig superfamily member related to CD28 and CTLA-4 which has been shown to negatively regulate antigen receptor signaling upon engagement of its ligands (PD-L1 and/or PD-L2) [29, 30]. The structure of murine PD-1 has been resolved [31]. PD-1 and family members are type I transmembrane glycoproteins containing an Ig Variable-type (V-type) domain responsible for ligand binding and a cytoplasmic tail which is responsible for the binding of signaling molecules. The cytoplasmic tail of PD-1 contains 2 tyrosine-based signaling motifs,

an immunoreceptor tyrosine-based inhibition motif (ITIM) and an immunoreceptor tyrosine-based switch motif (ITSM). Following T-cell stimulation, PD-1 recruits the tyrosine phosphatases SHP-1 and SHP-2 to the ITSM motif within its cytoplasmic tail, leading to the dephosphorylation of effector molecules such as CD3 $\zeta$ , PKC $\theta$  and ZAP70 which are involved in the CD3 T-cell signaling cascade [29, 32-34]. The mechanism by which PD-1 down modulates T-cell responses is similar to, but distinct from that of CTLA-4 as both molecules regulate an overlapping set of signaling proteins [35, 36]. PD-1 was shown to be expressed on activated lymphocytes including peripheral CD4<sup>+</sup> and CD8<sup>+</sup> T-cells, B-cells, T regs and Natural Killer cells [37, 38]. Expression has also been shown during thymic development on CD4-CD8- (double negative) T-cells as well as subsets of macrophages and dendritic cells [39]. The ligands for PD-1 (PD-L1 and PD-L2) are constitutively expressed or can be induced in a variety of cell types, including non-hematopoietic tissues as well as in various tumors [35, 40-42]. Both ligands are type I transmembrane receptors containing both IgV- and IgC-like domains in the extracellular region and contain short cytoplasmic regions with no known signaling motifs. Binding of either PD-1 ligand to PD-1 inhibits T-cell activation triggered through the T-cell receptor. PD-L1 is expressed at low levels on various non-hematopoietic tissues, most notably on vascular endothelium, whereas PD-L2 protein is only detectably expressed on antigen-presenting cells found in lymphoid tissue or chronic inflammatory environments. PD-L2 is thought to control immune T-cell activation in lymphoid organs, whereas PD-L1 serves to dampen unwarranted T-cell function in peripheral tissues [35]. Although healthy organs express little (if any) PD-L1, a variety of cancers were demonstrated to express abundant levels of this T-cell inhibitor. PD-1 has been suggested to regulate tumor-specific T-cell expansion in subjects with melanoma (MEL) [43]. This suggests that the PD-1/PD-L1 pathway plays a critical role in tumor immune evasion and should be considered as an attractive target for therapeutic intervention.

Pembrolizumab is a potent and highly selective humanized monoclonal antibody (mAb) of the IgG4/kappa isotype designed to directly block the interaction between PD-1 and its ligands, PD-L1 and PD-L2. Keytruda<sup>TM</sup> (pembrolizumab) has recently been approved in the United States for the treatment of patients with unresectable or metastatic melanoma and disease progression following ipilimumab and, if BRAF V600 mutation positive, a BRAF inhibitor.

## 1.2 Rationale

### 1.2.1 Dose Selection Rationale

The dose regimen of 200 mg Q3W of pembrolizumab is planned for all urothelial cancer trials. Available PK results in subjects with melanoma, NSCLC, and other solid tumor types support a lack of meaningful difference in PK exposures obtained at a given dose among tumor types. An open-label Phase 1 trial (PN001) in melanoma subjects is being conducted to evaluate the safety and clinical activity of single agent pembrolizumab. The dose escalation portion of this trial evaluated three dose levels, 1 mg/kg, 3 mg/kg, and 10 mg/kg, administered every 2 weeks (Q2W) in subjects with advanced solid tumors. All three dose levels were well tolerated and no dose-limiting toxicities were observed. This first in human study of pembrolizumab showed evidence of target engagement and objective evidence of

tumor size reduction at all dose levels (1 mg/kg, 3 mg/kg and 10 mg/kg Q2W). No maximum tolerated dose (MTD) has been identified.

In KEYNOTE-001, two randomized cohort evaluations of melanoma subjects receiving pembrolizumab at a dose of 2 mg/kg versus 10 mg/kg Q3W have been completed. The clinical efficacy and safety data demonstrate a lack of clinically important differences in efficacy response or safety profile at these doses. For example, in Cohort B2, advanced melanoma subjects who had received prior ipilimumab therapy were randomized to receive pembrolizumab at 2 mg/kg versus 10 mg/kg Q3W. The overall response rate (ORR) was 26% (21/81) in the 2mg/kg group and 26% (25/79) in the 10 mg/kg group (full analysis set (FAS)). The proportion of subjects with drug-related adverse events (AEs), grade 3-5 drug-related AEs, serious drug-related AEs, death or discontinuation due to an AE was comparable between groups or lower in the 10 mg/kg group.

Available pharmacokinetic results in subjects with melanoma, NSCLC, and other solid tumor types support a lack of meaningful difference in pharmacokinetic exposures obtained at a given dose among tumor types. Population PK analysis has been performed and has confirmed the expectation that intrinsic factors do not affect exposure to pembrolizumab to a clinically meaningful extent. Taken together, these data support the use of lower doses (with similar exposure to 2 mg/kg Q3W) in all solid tumor indications. 2 mg/kg Q3W is being evaluated in NSCLC in PN001, Cohort F30 and PN010, and 200 mg Q3W is being evaluated in head and neck cancer in PN012, which are expected to provide additional data supporting the dose selection.

Selection of 200 mg as the appropriate dose for a switch to fixed dosing is based on simulation results indicating that 200 mg will provide exposures that are reasonably consistent with those obtained with 2 mg/kg dose and importantly will maintain individual patient exposures within the exposure range established in melanoma as associated with maximal clinical response. A population PK model, which characterized the influence of body weight and other patient covariates on exposure, has been developed using available data from 476 subjects from PN001. The distribution of exposures from the 200 mg fixed dose are predicted to considerably overlap those obtained with the 2 mg/kg dose, with some tendency for individual values to range slightly higher with the 200 mg fixed dose. The slight increase in PK variability predicted for the fixed dose relative to weight-based dosing is not expected to be clinically important given that the range of individual exposures is well contained within the range of exposures shown in the melanoma studies of 2 and 10 mg/kg to provide similar efficacy and safety. The population PK evaluation revealed that there was no significant impact of tumor burden on exposure. In addition, exposure was similar between the NSCLC and melanoma indications. Therefore, there are no anticipated changes in exposure between different tumor types and indication settings.

### **1.2.2 Rationale for Endpoints**

The vast majority of patients with stage III NSCLC treated with chemoradiation will die from distant metastatic disease. The primary objective will be to assess whether pembrolizumab improves the time to metastatic disease. Immunotherapy is known to cause pseudo-progression (the appearance of local progression), and in patients treated with radiotherapy

followed by immunotherapy, it will be difficult to determine the significance of small changes in tumor size. This will make the measurement of PFS challenging and potentially unreliable. Therefore, in order to provide the most objective measure of drug efficacy, the time to distant metastatic disease has been chosen as the primary endpoint.

## **2. STUDY OBJECTIVES**

### **2.1. Primary Objective**

To determine if consolidation therapy with pembrolizumab following concurrent chemoradiation improves time to death or distant metastatic disease, depending on which occurs first, in subjects with inoperable or unresectable stage IIIA or IIIB NSCLC. Distant metastasis is defined as anything that is outside of the radiation field.

### **2.2. Secondary Objectives**

- To determine if consolidation therapy with pembrolizumab following concurrent chemoradiation improves PFS and OS in subjects with inoperable or unresectable stage IIIA or IIIB NSCLC.
- To assess toxicity and tolerability of pembrolizumab consolidation therapy following concurrent chemoradiation in subjects with stage IIIA or IIIB NSCLC.
- TTD in evaluable set

### **2.3. Exploratory Objectives**

- To assess PD-L1 expression levels in the tumors of subjects with stage IIIA or IIIB NSCLC and then correlate expression with PFS, OS, treatment toxicity, and tumor histology.

## **3. ELIGIBILITY CRITERIA**

### **3.1. Inclusion Criteria**

1. Written informed consent and HIPAA authorization for release of protected health information  
**NOTE:** HIPAA authorization may be included in the informed consent or obtained separately.
2. Age  $\geq$  18 years at the time of consent
3. Histological or cytological evidence of NSCLC
4. Must have unresectable or inoperable stage IIIA or IIIB disease. Subjects are considered unresectable or inoperable based on the judgment of the treating physician.

5. Subjects may have completed concurrent chemoradiation with a standard chemotherapy regimen (Cisplatin/Etoposide, Carboplatin/Paclitaxel or Cisplatin/Pemetrexed) and a dose of radiation ranging from 59.4-66.6 Gy. Subjects must have stable disease or disease response as evidenced on CT or PET scan evaluation. For those eligible, pembrolizumab should begin a minimum of 28 days and a maximum 56 days following the completion of chemoradiation **OR**
6. Subjects may have completed up to 2 cycles of consolidation therapy started within 4 weeks of completion of radiation. After completion of consolidation therapy, subjects must have stable disease or disease response as evidenced by CT or PET scan evaluation. For those eligible, pembrolizumab should begin 3-4 weeks after the last cycle of chemotherapy.
7. ECOG Performance Status of 0 or 1 within 14 days prior to registration for protocol therapy.
8. Adequate laboratory values obtained within 14 days prior to registration for protocol therapy (as defined in table 1 below).

9. Table 1 Adequate Organ Function Laboratory Values

System	Laboratory Value
<b>Hematological</b>	
Absolute neutrophil count (ANC)	$\geq 1,500$ /mcL
Platelets	$\geq 100,000$ / mcL
Hemoglobin	$\geq 9$ g/dL or $\geq 5.6$ mmol/L
<b>Renal</b>	
Serum creatinine <b>OR</b> Measured or calculated <sup>a</sup> creatinine clearance (GFR can also be used in place of creatinine or CrCl)	$\leq 1.5$ X upper limit of normal (ULN) <b>OR</b> $\geq 60$ mL/min for subject with creatinine levels $> 1.5$ X institutional ULN
<b>Hepatic</b>	
Serum total bilirubin	$\leq 1.5$ X ULN <b>OR</b> Direct bilirubin $\leq$ ULN for subjects with total bilirubin levels $> 1.5$ ULN
AST (SGOT) and ALT (SGPT)	$\leq 2.5$ X ULN
<b>Coagulation</b>	
International Normalized Ratio (INR) or Prothrombin Time (PT)	$\leq 1.5$ X ULN unless subject is receiving anticoagulant therapy as long as PT/INR/PTT is within therapeutic range of intended use of anticoagulants
<sup>a</sup> Creatinine clearance should be calculated per institutional standard.	

10. Women of childbearing potential must be willing to use two methods of contraception or abstain from heterosexual activity from the point of registration through 120 days after the last dose of study drug.
11. Male subjects of childbearing potential must agree to use an adequate method of contraception starting with the first dose of the study drug through 120 days after the last dose of the study drug.

### **3.2 Exclusion Criteria**

1. Pregnant or breastfeeding, or expecting to conceive or father children within the projected duration of the trial, starting with the pre-screening or screening visit through 120 days after the last dose of trial treatment.
2. Active central nervous system (CNS) metastases. Subjects must undergo a head computed tomography (CT) scan or brain MRI within 28 days prior to registration for protocol therapy to exclude brain metastases if symptomatic or without prior brain imaging.
3. Treatment with any investigational agent within 28 days prior to registration for protocol therapy.
4. Prior chemotherapy, adjuvant therapy, or radiotherapy for lung cancer other than standard concurrent chemoradiation or up to 2 cycles of consolidation as described above.
5. Prior therapy with a PD-1, PD-L1, PD-L2 or CTLA-4 inhibitor or a lung cancer-specific vaccine therapy
6. Presence of metastatic disease (stage IV NSCLC) is not allowed. Subjects must be evaluated with a CT or PET scan prior to registration for protocol therapy to exclude metastatic disease.
7. No active second cancers.
8. Evidence of active autoimmune disease requiring systemic treatment within the past 90 days or a documented history of clinically severe autoimmune disease, or a syndrome that requires systemic steroids or immunosuppressive agents. Subjects with vitiligo or resolved childhood asthma/atopy would be an exception to this rule. Subjects that require intermittent use of bronchodilators or local steroid injections would not be excluded from the study. Subjects with hypothyroidism stable on hormone replacement or Sjogren's syndrome will not be excluded from the study
9. Interstitial lung disease or history of pneumonitis requiring treatment with corticosteroids
10. Diagnosis of immunodeficiency or is receiving chronic systemic corticosteroid therapy or other immunosuppressive therapy (excludes inhaled corticosteroids) within 7 days of first dose of study drug



11. History of psychiatric illness or social situations that would limit compliance with study requirements
12. Clinically active infection as judged by the site investigator ( $\geq$  Grade 2 by CTCAE v4).
13. History of human immunodeficiency virus (HIV) infection or chronic hepatitis B or C.
14. Has a history or current evidence of any condition, therapy, or laboratory abnormality that might confound the results of the trial, interfere with the subject's participation for the full duration of the trial, or is not in the best interest of the subject to participate, in the opinion of the site investigator.
15. Has a known history of active TB (Bacillus Tuberculosis).
16. Hypersensitivity to pembrolizumab or any of its excipients.
17. Has received a live vaccine within 30 days prior to planned start of study therapy.  
Note: Seasonal influenza vaccines for injection are generally inactivated flu vaccines and are allowed; however intranasal influenza vaccines (e.g., Flu-Mist®) are live attenuated vaccines, and are not allowed.

#### **4. SUBJECT REGISTRATION**

All subjects must be registered through Hoosier Cancer Research Network (HCRN) electronic data capture (EDC) system prior to starting protocol therapy. A subject is considered to be registered to the protocol when an "On Study" date has been entered into the EDC System.

Subjects must begin therapy within **five business days** of the "on study" date.

#### **5. TREATMENT PLAN**

##### **5.1. Study Drug Administration and Treatment Schedule**

Table 2: Study Drug Administration

Drug	Dose	Frequency of administration	Route of administration	Number of weeks
Pembrolizumab	200 mg	Every 3 weeks	IV	Up to 52

Pembrolizumab 200 mg will be administered as a 30 minute IV infusion on Day 1 of each 21 day Cycle. Sites should make every effort to target infusion timing to be as close to 30 minutes as possible. However, given the variability of infusion pumps from site to site, a window of -five minutes and +10 minutes is permitted (i.e., infusion time is 30 minutes: -5 min/+10 min). Treatment will continue for up to 12 months, in the absence of prohibitive toxicities or disease progression.

The Pharmacy Manual contains specific instructions for the preparation of the pembrolizumab infusion fluid and administration of infusion solution.

#### **5.1.1 Dose Calculations**

The dose amount required to prepare the pembrolizumab infusion solution is a fixed dose (i.e., not based on the subject's weight) as per Table 2.

#### **5.1.2 Pre-medications**

No premedications are required prior to protocol therapy administration.

#### **5.1.3 Concomitant Medications**

Medications or vaccinations specifically prohibited in the exclusion criteria are not allowed during the ongoing trial. If there is a clinical indication for one of these or other medications or vaccinations specifically prohibited during the trial, discontinuation from trial therapy or vaccination may be required. The site investigator should discuss any questions regarding this with HCRN who will then communicate with the sponsor-investigator and Merck Clinical team regarding the situation. The final decision on any supportive therapy or vaccination rests with the site investigator and/or the subject's primary physician. There are no prohibited therapies during the Post-Treatment Follow-up Phase.

All treatments that the site investigator considers necessary for a subject's welfare may be administered at the discretion of the site investigator in keeping with the community standards of medical care. All concomitant medication will be recorded on the case report form (CRF) including all prescription, over-the-counter (OTC), herbal supplements, and IV medications and fluids. If changes occur during the trial period, documentation of drug dosage, frequency, route, and date may also be included on the CRF.

All concomitant medications received within 28 days before the first dose of trial treatment and 30 days after the last dose of trial treatment should be recorded. Concomitant medications administered more than 30 days after the last dose of trial treatment should be recorded for serious adverse events (SAE) and events of clinical interest (ECI) as defined in Section 11.1.6.

#### **5.1.4 Prohibited Concomitant Medications**

Subjects are prohibited from receiving the following therapies during the Screening and Treatment Phase of this trial:

- Antineoplastic systemic chemotherapy or biological therapy
- Immunotherapy not specified in this protocol
- Chemotherapy not specified in this protocol
- Investigational agents other than pembrolizumab
- Radiation therapy
- Live vaccines within 30 days prior to the first dose of trial treatment and while participating in the trial. Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, varicella/zoster, chicken pox, yellow fever, rabies, BCG, and typhoid (oral) vaccine. Seasonal influenza vaccines for injection are

- generally killed virus vaccines and are allowed; however intranasal influenza vaccines (e.g. Flu-Mist®) are live attenuated vaccines, and are not allowed.
- Systemic glucocorticoids for any purpose other than to modulate symptoms from an event of clinical interest of suspected immunologic etiology. The use of physiologic doses of corticosteroids may be approved after consultation with HCRN and the sponsor-investigator.

Subjects who, in the assessment by the site investigator, require the use of any of the aforementioned treatments for clinical management should be removed from the trial. The Exclusion Criteria describes other medications which are prohibited in this trial.

## **5.2 Evaluation of Adverse Events and Dose Modification**

The NCI Common Terminology Criteria for Adverse Events (CTCAE) v4 will be used to grade adverse events. Subjects enrolled in this study will be evaluated clinically and with standard laboratory tests before and at regular intervals during their participation in this study as specified in Section 7.

Subjects will be evaluated for adverse events (all grades) and adverse events requiring study drug interruption or discontinuation at each study visit for the duration of their participation in the study. Subjects discontinued from the treatment phase of the study for any reason will be evaluated at least 30 days ( $\pm 7$ ) after the last dose of study drug.

Table 3 Evaluating Adverse Event: A site investigator who is a qualified physician, will evaluate all adverse events as to determine:

<b>V4.0 CTCAE Grading</b>	<b>Grade 1</b>	<b>Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.</b>
	<b>Grade 2</b>	<b>Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL.</b>
	<b>Grade 3</b>	<b>Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL.</b>
	<b>Grade 4</b>	<b>Life threatening consequences; urgent intervention indicated.</b>
	<b>Grade 5</b>	<b>Death related to AE</b>
<b>Seriousness</b>	A serious adverse event is any adverse event: †Results in death; or †Is life threatening; or places the subject, in the view of the site investigator, at immediate risk of death from the event as it occurred (Note: This does not include an adverse event that, had it occurred in a more severe form, might have caused death.); or †Results in a persistent or significant disability/incapacity (substantial disruption of one's ability to conduct normal life functions); or †Results in or prolongs an existing inpatient hospitalization (hospitalization is defined as an inpatient admission, regardless of length of stay, even if the hospitalization is a precautionary measure for continued observation. (Note: Hospitalization [including hospitalization for an elective procedure] for a preexisting condition which has not worsened does not constitute a serious adverse event.); or †Is a congenital anomaly/birth defect (in offspring of subject taking the product regardless of time to diagnosis); or Is a new cancer; (that is not a condition of the study) or Is an overdose (whether accidental or intentional). Any adverse event associated with an overdose is considered a serious adverse event. An overdose that is not associated with an adverse event is considered a non-serious event of clinical interest and must be reported within 24 hours. Other important medical events that may not result in death, not be life threatening, or not require hospitalization may be considered a serious adverse event when, based upon appropriate medical judgment, the event may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed previously (designated above by a †).	
<b>Duration</b>	Record the start and stop dates of the adverse event. If less than 1 day, indicate the appropriate length of time and units	
<b>Action taken</b>	Did the adverse event cause the Merck product to be discontinued?	
<b>Relationship to test drug</b>	Did the Merck product cause the adverse event? The determination of the likelihood that the Merck product caused the adverse event will be provided by a site investigator who is a qualified physician. The site investigator's signed/dated initials on the source document or worksheet that supports the causality noted on the AE form, ensures that a medically qualified assessment of causality was done. This initialed document must be retained for the required regulatory time frame. The criteria below are intended as reference guidelines to assist the site investigator in assessing the likelihood of a relationship between the test drug and the adverse event based upon the available information. <b>The following components are to be used to assess the relationship between the Merck product and the AE;</b> the greater the correlation with the components and their respective elements (in number and/or intensity), the more likely the Merck product caused the adverse event (AE):	
	<b>Exposure</b>	Is there evidence that the subject was actually exposed to the Merck product such as: reliable history, acceptable compliance assessment (pill count, diary, etc.), expected pharmacologic effect, or measurement of drug/metabolite in bodily specimen?
	<b>Time Course</b>	Did the AE follow in a reasonable temporal sequence from administration of the Merck product? Is the time of onset of the AE compatible with a drug-induced effect (applies to trials with investigational medicinal product)?
	<b>Likely Cause</b>	Is the AE not reasonably explained by another etiology such as underlying disease, other drug(s)/vaccine(s), or other host or environmental factors

Relationship to Merck product (continued)	The following components are to be used to assess the relationship between the test drug and the AE: (continued)	
	<b>Dechallenge</b>	Was the Merck product discontinued or dose/exposure/frequency reduced? If yes, did the AE resolve or improve? If yes, this is a positive dechallenge. If no, this is a negative dechallenge. (Note: This criterion is not applicable if: (1) the AE resulted in death or permanent disability; (2) the AE resolved/improved despite continuation of the Merck product; or (3) the trial is a single-dose drug trial); or (4) Merck product(s) is/are only used one time.)
	<b>Rechallenge</b>	Was the subject re-exposed to the Merck product in this study? If yes, did the AE recur or worsen? If yes, this is a positive rechallenge. If no, this is a negative rechallenge. (Note: This criterion is not applicable if: (1) the initial AE resulted in death or permanent disability, or (2) the trial is a single-dose drug trial); or (3) Merck product(s) is/are used only one time). NOTE: IF A RECHALLENGE IS PLANNED FOR AN ADVERSE EVENT WHICH WAS SERIOUS AND WHICH MAY HAVE BEEN CAUSED BY THE MERCK PRODUCT, OR IF REEXPOSURE TO THE MERCK PRODUCT POSES ADDITIONAL POTENTIAL SIGNIFICANT RISK TO THE SUBJECT, THEN THE RECHALLENGE MUST BE APPROVED IN ADVANCE BY THE U.S. CLINICAL MONITOR AS PER DOSE MODIFICATION GUIDELINES IN THE PROTOCOL.
	<b>Consistency with Trial Treatment Profile</b>	Is the clinical/pathological presentation of the AE consistent with previous knowledge regarding the Merck product or drug class pharmacology or toxicology?
The assessment of relationship will be reported on the case report forms /worksheets by a site investigator who is a qualified physician according to his/her best clinical judgment, including consideration of the above elements.		
<b>Record one of the following</b>		<b>Use the following scale of criteria as guidance (not all criteria must be present to be indicative of a Merck product relationship).</b>
<b>Yes, there is a reasonable possibility of Merck product relationship.</b>		There is evidence of exposure to the Merck product. The temporal sequence of the AE onset relative to the administration of the Merck product is reasonable. The AE is more likely explained by the Merck product than by another cause.
<b>No, there is not a reasonable possibility Merck product relationship</b>		Subject did not receive the Merck product OR temporal sequence of the AE onset relative to administration of the Merck product is not reasonable OR there is another obvious cause of the AE. (Also entered for a subject with overdose without an associated AE.)

### 5.2.1 Definition of treatment-limiting adverse events

A treatment-limiting adverse event is any adverse event related to study drug experienced during the study resulting in treatment termination.

### 5.2.2 Dose Modifications and Toxicity Management

Pembrolizumab will be withheld for drug-related Grade 4 hematologic toxicities, non-hematological toxicity  $\geq$  Grade 3 including laboratory abnormalities, and severe or life-threatening AEs as per Table 4 below.

Table 4: Dose modification guidelines for drug-related adverse events.

Toxicity	Grade	Hold Treatment (Y/N)	Timing for restarting treatment	Dose/Schedule for restarting treatment	Discontinue Subject (after consultation with HCRN and sponsor-investigator)
Hematological Toxicity	1, 2	No	N/A	N/A	N/A
	3* *Excluding Grade 3 neutropenia, anemia, and thrombocytopenia	Yes	Toxicity resolves to Grade 0-1 or baseline	May increase the dosing interval by 1 week (permanent change)	Toxicity does not resolve within 12 weeks of last infusion <i>Permanent discontinuation should be considered for any severe or life-threatening event</i>
	4	Yes	Toxicity resolves to Grade 0-1 or baseline	May increase the dosing interval by 1 week (permanent change)	
Non-hematological toxicity	1	No	N/A	N/A	N/A
<p>Note: Exception to be treated similar to grade 1 toxicity</p> <ul style="list-style-type: none"> <li>Grade 2 alopecia</li> <li>Grade 2 fatigue</li> </ul> <p>For additional information regarding Adverse Events with a potential Immune-Etiology see Section 5.3.</p>	2	Consider withholding for persistent symptoms	Toxicity resolves to Grade 0-1 or baseline	<p><i>Clinical AE resolves within 4 weeks:</i> Same dose and schedule (see Section 5.3 for recommendations regarding pneumonitis)</p> <p><i>Clinical AE does not resolve within 4 weeks:</i> May increase the dosing interval by 1 week for each occurrence</p>	Toxicity does not resolve within 12 weeks of last infusion

Toxicity	Grade	Hold Treatment (Y/N)	Timing for restarting treatment	Dose/Schedule for restarting treatment	Discontinue Subject (after consultation with HCRN and sponsor-investigator)
	3, 4	Yes	Toxicity resolves to Grade 0-1 or baseline	May increase the dosing interval by 1 week for each occurrence	Toxicity does not resolve within 12 weeks of last infusion <i>Permanent discontinuation should be considered for any severe or life-threatening event</i>

In case toxicity does not resolve to Grade 0-1 within 12 weeks after last infusion, trial treatment should be discontinued after consultation with HCRN and the sponsor-investigator. With site investigator and sponsor-investigator agreement, subjects with a laboratory adverse event still at Grade 2 after 12 weeks may continue treatment in the trial only if asymptomatic and controlled. For information on the management of adverse events, see Section 5.3.1. If a subject has more than 3 delays in study drug dosing due to other toxicities they will be discontinued from the trial treatment.

Subjects who experience a recurrence of the same severe or life-threatening event at the same grade or greater with re-challenge of pembrolizumab should be discontinued from trial treatment.

### 5.3 Rescue Medications & Supportive Care

#### 5.3.1 Supportive Care Guidelines

Subjects should receive appropriate supportive care measures as deemed necessary by the site investigator. Suggested supportive care measures for the management of adverse events with potential immunologic etiology are outlined below. Where appropriate, these guidelines include the use of oral or intravenous treatment with corticosteroids as well as additional anti-inflammatory agents if symptoms do not improve with administration of corticosteroids. Note that several courses of steroid tapering may be necessary as symptoms may worsen when the steroid dose is decreased. For each disorder, attempts should be made to rule out other causes such as metastatic disease or bacterial or viral infection, which might require additional supportive care. The treatment guidelines are intended to be applied when the investigator determines the events to be related to pembrolizumab.

Note: if after the evaluation the event is determined not to be related, the investigator is instructed to follow the ECI reporting guidelines. It may be necessary to perform conditional procedures such as bronchoscopy, endoscopy, or skin photography as part of evaluation of the event.

- **Nausea/vomiting:** Nausea and vomiting should be treated aggressively, and consideration should be given in subsequent cycles to the administration of prophylactic antiemetic therapy according to standard institutional practice. Subjects should be strongly encouraged to maintain liberal oral fluid intake.
- **Anti-infectives:** Subjects with a documented infectious complication should receive oral or IV antibiotics or other anti-infective agents as considered appropriate by the site investigator for a given infectious condition, according to standard institutional practice.
- **Diarrhea: /Colitis:**

Subjects should be carefully monitored for signs and symptoms of enterocolitis (such as diarrhea, abdominal pain, blood or mucus in stool, with or without fever) and of bowel perforation (such as peritoneal signs and ileus).

  - All subjects who experience diarrhea/colitis should be advised to drink liberal quantities of clear fluids. If sufficient oral fluid intake is not feasible, fluid and electrolytes should be substituted via IV infusion. For Grade 2 or higher diarrhea, consider GI consultation and endoscopy to confirm or rule out colitis.
  - For Grade 2 diarrhea/colitis that persists greater than 3 days, administer oral corticosteroids.
  - For Grade 3 or 4 diarrhea/colitis that persists > 1 week, treat with intravenous steroids followed by high dose oral steroids.
  - When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks.
- **Type 1 diabetes mellitus (if new onset, including diabetic ketoacidosis [DKA]) or ≥ Grade 3 Hyperglycemia, if associated with ketosis (ketonuria) or metabolic acidosis (DKA)**
  - For T1DM or Grade 3-4 Hyperglycemia
    - Insulin replacement therapy is recommended for Type I diabetes mellitus and for Grade 3-4 hyperglycemia associated with metabolic acidosis or ketonuria.
    - Evaluate subjects with serum glucose and a metabolic panel, urine ketones, glycosylated hemoglobin, and C-peptide.
- **Hypophysitis:**
  - For Grade 2 events, treat with corticosteroids. When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks. Replacement of appropriate hormones may be required as the steroid dose is tapered.
  - For Grade 3-4 events, treat with an initial dose of IV corticosteroids followed by oral corticosteroids. When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks. Replacement of appropriate hormones may be required as the steroid dose is tapered.



- **Hyperthyroidism or Hypothyroidism:**  
Thyroid disorders can occur at any time during treatment. Monitor subjects for changes in thyroid function (at the start of treatment, periodically during treatment, and as indicated based on clinical evaluation) and for clinical signs and symptoms of thyroid disorders.
  - Grade 2 hyperthyroidism events (and Grade 2-4 hypothyroidism):
    - In hyperthyroidism, non-selective beta-blockers (e.g. propranolol) are suggested as initial therapy.
    - In hypothyroidism, thyroid hormone replacement therapy, with levothyroxine or liothyronine, is indicated per standard of care.
  - Grade 3-4 hyperthyroidism
    - Treat with an initial dose of IV corticosteroid followed by oral corticosteroids. When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks. Replacement of appropriate hormones may be required as the steroid dose is tapered.
  
- **Hepatic:**
  - For Grade 2 events, monitor liver function tests more frequently until returned to baseline values (consider weekly).
    - Treat with IV or oral corticosteroids
  - For Grade 3-4 events, treat with intravenous corticosteroids for 24 to 48 hours.
  - When symptoms improve to Grade 1 or less, a steroid taper should be started and continued over no less than 4 weeks.
  
- **Renal Failure or Nephritis:**
  - For Grade 2 events, treat with corticosteroids.
  - For Grade 3-4 events, treat with systemic corticosteroids.
  - When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks.
  
- **Management of Infusion Reactions:** Acute infusion reactions (which can include cytokine release syndrome, angioedema, or anaphylaxis) are different from allergic/hypersensitive reactions, although some of the manifestations are common to both AEs.

Table 5 below shows treatment guidelines for subjects who experience an infusion reaction associated with administration of pembrolizumab.

NCI CTCAE Grade	Treatment	Premedication at subsequent dosing
<u>Grade 1</u> Mild reaction; infusion interruption not indicated; intervention not indicated	Increase monitoring of vital signs as medically indicated until the subject is deemed medically stable in the opinion of the investigator.	None
<u>Grade 2</u> Requires infusion interruption but responds promptly to symptomatic treatment (e.g., antihistamines, NSAIDS, narcotics, IV fluids);	<b>Stop Infusion and monitor symptoms.</b> Additional appropriate medical therapy may include but is not limited to: IV fluids Antihistamines NSAIDS Acetaminophen	Subject may be premedicated 1.5h (± 30 minutes) prior to infusion of pembrolizumab with:  Diphenhydramine 50 mg po (or equivalent dose of antihistamine).

NCI CTCAE Grade	Treatment	Premedication at subsequent dosing
prophylactic medications indicated for <=24 hrs	<p>Narcotics</p> <p>Increase monitoring of vital signs as medically indicated until the subject is deemed medically stable in the opinion of the investigator.</p> <p>If symptoms resolve within one hour of stopping drug infusion, the infusion may be restarted at 50% of the original infusion rate (e.g., from 100 mL/hr to 50 mL/hr). Otherwise dosing will be held until symptoms resolve and the subject should be premedicated for the next scheduled dose.</p> <p><b>Subjects who develop Grade 2 toxicity despite adequate premedication should be permanently discontinued from further trial treatment administration.</b></p>	Acetaminophen 500-1000 mg po (or equivalent dose of antipyretic).
<p><u>Grades 3 or 4</u></p> <p>Grade 3: Prolonged (i.e., not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for other clinical sequelae (e.g., renal impairment, pulmonary infiltrates)</p> <p>Grade 4: Life-threatening; pressor or ventilatory support indicated</p>	<p><b>Stop Infusion.</b></p> <p>Additional appropriate medical therapy may include but is not limited to:</p> <ul style="list-style-type: none"> <li>IV fluids</li> <li>Antihistamines</li> <li>NSAIDS</li> <li>Acetaminophen</li> <li>Narcotics</li> <li>Oxygen</li> <li>Pressors</li> <li>Corticosteroids</li> <li>Epinephrine</li> </ul> <p>Increase monitoring of vital signs as medically indicated until the subject is deemed medically stable in the opinion of the investigator.</p> <p>Hospitalization may be indicated.</p> <p><b>Subject is permanently discontinued from further trial treatment administration.</b></p>	No subsequent dosing
Appropriate resuscitation equipment should be available in the room and a physician readily available during the period of drug administration.		

### 5.3.2 Supportive Care Guidelines for Pneumonitis

Subjects with symptomatic pneumonitis should immediately stop receiving Pembrolizumab and have an evaluation. The evaluation may include bronchoscopy and pulmonary function tests to rule out other causes such as infection. If the subject is determined to have study drug associated pneumonitis, the suggested treatment plan is detailed in Table 7.

Table 7: Recommended Approach to Handling Pneumonitis

Study drug associated pneumonitis	Withhold/Discontinue Pembrolizumab	Supportive Care
Grade 1 (asymptomatic)	No action	Intervention not indicated
Grade 2*	Withhold pembrolizumab; may return to treatment if improves to Grade 1 or resolves within 12 weeks	Systemic corticosteroids are indicated. When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks.
Grade 3 and Grade 4	Discontinue pembrolizumab	Systemic corticosteroids are indicated. The use of infliximab may be indicated as appropriate. Add prophylactic antibiotics for opportunistic infections in the case of prolonged steroid administration.

\*For Grade 2 pneumonitis that improves to  $\leq$  Grade 1 within 12 weeks, the following rules should apply:

- First episode of pneumonitis
  - May increase dosing interval by one week in subsequent cycles (permanent change)
- Second episode of pneumonitis – permanently discontinue pembrolizumab if upon rechallenge subject develops pneumonitis  $\geq$  Grade 2

## 5.4 Diet/Activity/Other Considerations

### 5.4.1 Diet

Subjects should maintain a normal diet unless modifications are required to manage an AE such as diarrhea, nausea or vomiting.

### 5.4.2 Contraception

Pembrolizumab may have adverse effects on a fetus in utero. Furthermore, it is not known if pembrolizumab has transient adverse effects on the composition of sperm. Non-pregnant, non-breast-feeding women may be enrolled if they are willing to use 2 methods of birth control or are considered highly unlikely to conceive. Highly unlikely to conceive is defined as 1) surgically sterilized, or 2) postmenopausal (a woman who is  $\geq 45$  years of age and has not had menses for greater than 1 year will be considered postmenopausal), or 3) not heterosexually active for the duration of the study. The two birth control methods can be either two barrier methods or a barrier method plus a hormonal method to prevent pregnancy. Subjects should start using birth control from study Visit 1 throughout the study period up to 120 days after the last dose of study therapy.

The following are considered adequate barrier methods of contraception: diaphragm, condom (by the partner), copper intrauterine device, sponge, or spermicide. Appropriate hormonal contraceptives will include any registered and marketed contraceptive agent that contains an estrogen and/or a progestational agent (including oral, subcutaneous, intrauterine, or intramuscular agents).

Subjects should be informed that taking the study medication may involve unknown risks to the fetus (unborn baby) if pregnancy were to occur during the study. In order to participate in the study they must adhere to the contraception requirement (described above) for the duration of the study and during the follow-up period defined in section 11.4. If there is any question that a subject will not reliably comply with the requirements for contraception, that subject should not be entered into the study.

### 5.4.3 Use in Pregnancy

If a subject inadvertently becomes pregnant while on treatment with pembrolizumab, the subject will immediately be removed from the study. The site will contact the subject at least monthly and document the subject's status until the pregnancy has been completed or terminated. The outcome of the pregnancy will be reported to HCRN **within 24 hours** of discovery of event and HCRN will notify the sponsor-investigator **within 1 business day** and Merck **within 2 business days** if the outcome is a serious adverse experience (e.g., death, abortion, congenital anomaly, or

other disabling or life-threatening complication to the mother or newborn). . The site investigator will make every effort to obtain permission to follow the outcome of the pregnancy and report the condition of the fetus or newborn to HCRN who will report to Merck. If a male subject impregnates his female partner the study personnel at the site must be informed immediately and the pregnancy reported to the HCRN who will report the event to Merck and followed as described above and in Section 11.4.

#### **5.4.4 Use in Nursing Women**

It is unknown whether pembrolizumab is excreted in human milk. Since many drugs are excreted in human milk, and because of the potential for serious adverse reactions in the nursing infant, subjects who are breast-feeding are not eligible for enrollment.

### **6. TREATMENT DISCONTINUATION**

#### **6.1. Subject Withdrawal/Discontinuation Criteria**

Subjects may withdraw consent at any time for any reason or be withdrawn from the trial at the discretion of the site investigator should any untoward effect occur. In addition, a subject may be withdrawn by the sponsor-investigator or HCRN if enrollment into the trial is inappropriate, the trial plan is violated, or for administrative and/or other safety reasons. Specific details regarding discontinuation or withdrawal are provided below.

A subject must be discontinued from the trial treatment for any of the following reasons:

- Confirmed radiographic disease progression by RECIST 1.1 criteria
- Unacceptable adverse experiences as described in Section 5.2.3
- Intercurrent illness that prevents further administration of treatment
- Site investigator's decision to withdraw the subject
- The subject has a confirmed positive serum/urine pregnancy test
- Noncompliance with trial treatment or procedure requirements
- Completed 12 months of treatment with pembrolizumab
- Subject refuses further treatment

A subject must be discontinued from the trial for any of the following reasons:

- Administrative reasons
- The subject or legal representative (such as a parent or legal guardian) withdraws consent.
- The subject is lost to follow-up

The End of Treatment and Follow-up visit procedures are listed in Section 7 (Study Schedule of Events and Visit Requirements). After the end of treatment, each subject will be followed for 30 days for adverse event monitoring (serious adverse events will be collected for 90 days after the end of treatment as described in Section 11.2.2). Subjects who discontinue for reasons other than progressive disease will have post-treatment follow-up for disease status until disease progression, initiating a non-study cancer treatment, withdrawing consent or becoming lost to follow-up. After documented disease progression each subject will be followed for overall survival until death, withdrawal of consent, or the end of the study, whichever occurs first.

When a subject discontinues/withdraws prior to trial completion, all applicable activities scheduled for the final trial visit should be performed at the time of discontinuation. Any adverse events which are present at the time of discontinuation/withdrawal should be followed in accordance with the safety requirements outlined in Section 11.2.1 – AE Reporting). Subjects who a) attain a CR or b) complete 12 months of treatment with pembrolizumab will discontinue treatment. After discontinuing treatment, following assessment of CR, these subjects should return to the site for a Safety Follow-up Visit and then proceed to the Follow-Up Period of the study.

## 7. STUDY SCHEDULE OF EVENTS

Examination	Screening		On Treatment Cycle 1+ (± 3) Cycle = 21 days			EOT	Follow up <sup>8</sup>
	-28 days	-14 days	Day 1	Day 8	Day 15	30 days (±7) after last dose	(±14 days)
<b>REQUIRED ASSESSMENTS</b>							
Informed Consent	X						
Medical history and Height		X					
Physical examination including vital signs (blood pressure, weight)		X	X			X	
ECOG performance status		X	X			X	
AEs & concomitant medications <sup>1</sup>		X	X			X	X
<b>LABORATORY TESTING</b>							
CBC with differential and platelet ct		X	X <sup>5</sup>			X	
Complete Metabolic Profile		X	X <sup>5</sup>			X	
Direct bilirubin, Mg, Phos		X	X <sup>5</sup>			X	
Measured or calculated creatinine clearance (GFR can also be used in place of serum creatinine or CrCl)		X					
PT/INR and aPTT		X					
Thyroid function (TSH, T3 and T4)		X	X <sup>5</sup>				
Serum or Urine pregnancy test <sup>4</sup>		X <sup>4</sup>					
<b>DISEASE ASSESSMENT</b>							
Pathology Report of diagnosis	X <sup>2</sup>						
CT of chest/abdomen or PET CT	X <sup>3</sup>		CT chest/abd or PET/CT every 9 weeks during treatment				X <sup>8</sup>
CT or MRI Brain <sup>9</sup>	X						
<b>TREATMENT EXPOSURE</b>							
Pembrolizumab			X <sup>6</sup>				
<b>CORRELATIVE STUDIES</b>							
Optional Unstained Slide Submission for PD-L1 Analysis			X <sup>7</sup>				
<b>FOLLOW-UP</b>							
Progression and survival <sup>8</sup>							X

1. Treatment-related adverse events will be followed until resolution, return to baseline, or deemed clinically insignificant. Adverse events (from time of consent) and concomitant medications (28 days prior to start of protocol treatment) should be assessed and recorded until 30 days after last dose of pembrolizumab. . SAE's and the conmeds used to treat them will be collected up to 90 days post treatment.
2. A pathology report confirming the diagnosis of NSCLC must be obtained and reviewed by the treating physician prior to registration to study.
3. Screening scan including at least CT portion of the chest and abdomen must be a minimum of 28 days and a maximum of 56 days following the completion of chemoradiation. PET CT may be done in place of regular CT scans at the discretion of the site investigator. Scans should be done within 28 days prior to treatment initiation. A head CT or MRI will be performed within 28 days of treatment initiation if subject is symptomatic or no prior brain imaging done.
4. For women of childbearing potential only. This must be completed and negative within 7 days of registration for protocol therapy.
5. C1D1 testing does not need to be repeated if performed within 7 days of starting protocol therapy.
6. For subjects who meet all eligibility criteria and have recovered sufficiently from treatment with chemoradiation, initial consolidation therapy with pembrolizumab will be started a minimum of 28 days and a maximum of 56 days after chemoradiation is complete. For subjects who meet all eligibility criteria after completion of up to two consolidation treatments, therapy with pembrolizumab will be started 3-4 weeks after last cycle of chemotherapy. Treatment with a fixed dose of 200mg IV of pembrolizumab will occur on day 1 of each 3 week cycle until progressive disease or unacceptable toxicity develop or until the subject has completed 52 weeks of therapy with pembrolizumab.
7. Optional submission of unstained slides from an archived tumor block for PD-L1 analysis. See SPM for collection, labeling and shipping instructions.
8. After completion of pembrolizumab subjects who discontinue for reasons other than progressive disease will have post-treatment follow-up for disease status until disease progression, initiating a non-study cancer treatment, withdrawing consent or becoming lost to follow-up. After documented disease progression each subject will be followed for overall survival until death, withdrawal of consent, or the end of the study (whichever occurs first). Radiographic disease assessment will be done every 9 weeks during study treatment. Once treatment is complete, radiographic disease assessment should be performed every 3 months during year 1 and 2 then every 6 months during year 3-5 then annually thereafter. PET CT may be done in place of regular CT scans at the discretion of the site investigator. This imaging may be done locally.
9. A head MRI or CT should be done prior to study treatment for subjects that are symptomatic or have not had prior brain imaging.

## **7.1 Screening**

### **7.1.1 Within 28 days of study registration**

- Informed consent
- Pathology Report Confirmation. A pathology report confirming the diagnosis of NSCLC must be obtained and reviewed by the treating physician prior to registration to the study.
- Radiology Imaging: A CT of the chest and abdomen will be done a minimum of 28 days and a maximum of 56 days after chemoradiation. This imaging will be done within 28 days of treatment initiation on study. A PET CT may be done instead of regular CT scans. A head MRI or CT should be done for subjects that are symptomatic or have not had prior brain imaging of study treatment.
- Optional archived tumor block to obtain slides from for PD-L1 analysis. See SPM for collection, labeling and shipping instructions.

### **7.1.2 Within 14 days of study registration**

- Medical History
- Height
- Physical examination including vital signs (blood pressure, weight)
- ECOG performance status
- Complete Metabolic Profile to include Na, K, Cl, CO<sub>2</sub>, total bilirubin, direct bilirubin, total protein, albumin, alk phos, AST, ALT, serum creatinine, BUN, calcium, Mg, Phos, and glucose. Please see Table 1 for additional information regarding serum creatinine, calculated creatinine clearance and GFR values.
- Complete Blood Count with differential to include absolute neutrophil count (ANC), platelets and hemoglobin
- PT/INR and aPTT
- Thyroid function (TSH, T3 and T4)
- **Within 7 days:** Serum or urine pregnancy test for women of childbearing potential.
- Adverse events and concomitant medications. This also includes events of clinical interest.

## **7.1. On Treatment**

### **7.2.1 Day 1 of each Cycle unless otherwise specified**

- Physical examination including vital signs (blood pressure, weight)
- ECOG performance status
- Complete Metabolic Profile to include Na, K, Cl, CO<sub>2</sub>, total bilirubin, direct bilirubin, total protein, albumin, alk phos, AST, ALT, creatinine, BUN, calcium, Mg, Phos, and glucose (For C1D1 do not repeat if screening CMP within 7 days of starting protocol therapy)
- Complete Blood Count with differential to include absolute neutrophil count (ANC), platelet and hemoglobin (For C1D1 do not repeat if screening CMP within 7 days of starting protocol therapy).
- Thyroid function (TSH, T3 and T4) (For C1D1 do not repeat if screening CMP within 7 days of starting protocol therapy).



- Adverse events and concomitant medications. This also includes events of clinical interest.
- Pembrolizumab 200 mg IV for up to 52 weeks

#### **7.2. End of Treatment (EOT) (30 days after last dose of study drug $\pm$ 7 days)**

- Physical examination including vital signs (blood pressure, weight)
- ECOG performance status
- Complete Metabolic Profile to include Na, K, Cl, CO<sub>2</sub>, total bilirubin, direct bilirubin, total protein, albumin, alk phos, AST, ALT, creatinine, BUN, calcium, Mg, Phos, and glucose
- Complete Blood Count with differential to include absolute neutrophil count (ANC), platelet and hemoglobin
- Adverse events and concomitant medications must be assessed. Events of clinical interest (ECIs) and serious adverse events must be assessed at least 90 days after dose of study drug (+7 days).

#### **7.3. Follow-up ( $\pm$ 14 days)**

After completion of pembrolizumab, subjects who discontinue for reasons other than progressive disease will have post-treatment follow-up for disease status until disease progression, initiating a non-study cancer treatment, withdrawing consent or becoming lost to follow-up. After documented disease progression each subject will be followed for overall survival until death, withdrawal of consent, or the end of the study (whichever occurs first).

- Adverse events. Follow treatment-related adverse events until resolution, return to baseline, or deemed clinically insignificant. This also includes events of clinical interest.
- Radiographic disease assessment should be performed every 3 months during year 1 and 2 then every 6 months during year 3-5 then annually thereafter. PET CT may be done in place of regular CT scans at the discretion of the site investigator. This imaging may be done locally.

### **8. CRITERIA FOR DISEASE EVALUATION**

Response assessments will be made both using the Immune Related Response Criteria, and using RECIST v1.1, allowing additional comparisons among these criteria for disease response assessment. The same measurable and non-measurable lesions will be followed by both RECIST v1.1 & irRC. RECIST 1.1 will be used to determine the primary objective of the trial and RECIST 1.1 and Immune Related Response Criteria will be used in secondary objective of PFS.

#### **8.1. Immune Related Response Criteria:**

This study will utilize the Immune Related Response Criteria (irRC). These response criteria were developed to overcome the variable and unusual patterns of response to immunotherapeutic agents, in particular, ipilimumab [44]. The development of the guidelines were prompted by observations, mostly in subjects with metastatic melanoma, of initial disease progression followed by later response, late responses, and mixed responses with an overall decrease in tumor burden.

### 8.1.1. Antitumor response based on total measurable tumor burden

For the irRC, only index and measurable new lesions are taken into account (in contrast to conventional WHO criteria, which do not require the measurement of new lesions, nor do they include new lesion measurements in the characterization of evolving tumor burden). At the baseline tumor assessment, the sum of the products of the two largest perpendicular diameters (SPD) of all index lesions (five lesions per organ, up to 10 visceral lesions) is calculated. At each subsequent tumor assessment, the SPD of the index lesions and of new, measurable lesions (up to 5 new lesions per organ; 10 visceral lesions) are added together to provide the total tumor burden:  $\text{Tumor Burden} = \text{SPD}_{\text{index lesions}} + \text{SPD}_{\text{new, measurable lesions}}$

**Table 8: Comparison of WHO and irRC criteria**

	WHO	irRC
New, measurable lesions	Always represent PD	Incorporated into tumor burden
New, nonmeasurable lesions	Always represent PD	Do not define progression (but preclude irCR)
Non-index lesions	Changes contribute to defining BOR of CR, PR, SD, and PD	Contribute to defining irCR (complete disappearance required)
CR	Disappearance of all lesions in two consecutive observations not less than 4 wk apart	Disappearance of all lesions in two consecutive observations not less than 4 wk apart
PR	$\geq 50\%$ decrease in SPD of all index lesions compared with baseline in two observations at least 4 wk apart, in absence of new lesions or unequivocal progression of non-index lesions	$\geq 50\%$ decrease in tumor burden compared with baseline in two observations at least 4 wk apart
SD	50% decrease in SPD compared with baseline cannot be established nor 25% increase compared with nadir, in absence of new lesions or unequivocal progression of non-index lesions	50% decrease in tumor burden compared with baseline cannot be established nor 25% increase compared with nadir
PD	At least 25% increase in SPD compared with nadir and/or unequivocal progression of non-index lesions and/or appearance of new lesions (at any single time point)	At least 25% increase in tumor burden compared with nadir (at any single time point) in two consecutive observations at least 4 wk apart

### 8.1.2. Time-point response assessment using irRC

Percentage changes in tumor burden per assessment time point describe the size and growth kinetics of both conventional and new, measurable lesions as they appear. At each tumor assessment, the response in index and new, measurable lesions is defined based on the change in tumor burden (after ruling out irPD). Decreases in tumor burden must be assessed relative to baseline measurements (i.e., the SPD of all index lesions at screening). The irRC were derived from WHO criteria and, therefore, the thresholds of response remain the same. However, the irRC response categories have been modified from those of WHO criteria as detailed in Tables 8 and 9.

### 8.1.3. Overall response using the irRC

The sum of the products of diameters at tumor assessment using the immune-related response criteria (irRC) for progressive disease incorporates the contribution of new measurable lesions. Each net Percentage Change in Tumor Burden per assessment using irRC criteria accounts for the size and growth kinetics of both old and new lesions as they appear.

#### Definition of Index Lesions Response Using irRC

- **irComplete Response (irCR):** Complete disappearance of all *index* lesions. This category encompasses exactly the same subjects as “CR” by the mWHO criteria.
- **irPartial Response (irPR):** Decrease, relative to baseline, of 50% or greater in the sum of the products of the two largest perpendicular diameters of all *index* and all new measurable lesions (ie., Percentage Change in Tumor Burden). Note: the appearance of new measurable lesions is factored into the overall tumor burden, but does not automatically qualify as progressive disease until the SPD increases by  $\geq 25\%$  when compared to SPD at nadir.
- **irStable Disease (irSD):** Does not meet criteria for irCR or irPR, in the absence of progressive disease.
- **irProgressive Disease (irPD):** At least 25% increase Percentage Change in Tumor Burden (i.e., taking sum of the products of all *index* lesions and any new lesions) when compared to SPD at nadir.

#### Definition of Non-Index Lesions Response Using irRC

- **irComplete Response (irCR):** Complete disappearance of all *non-index* lesions. This category encompasses exactly the same subjects as “CR” by the mWHO criteria.
- **irPartial Response (irPR) or irStable Disease (irSD):** *non-index* lesion(s) are not considered in the definition of PR, these terms do not apply.
- **irProgressive Disease (irPD):** Increases in number or size of *non-index* lesion(s) does not constitute progressive disease unless/until the Percentage Change in Tumor Burden increases by 25% (i.e., the SPD at nadir of the index lesions increases by the required amount).

#### Impact of New Lesions on irRC

New lesions in and by themselves do not qualify as progressive disease. However their contribution to total tumor burden is included in the SPD which in turn feeds into the irRC criteria for tumor response. Therefore, new non-measurable lesions will not discontinue any subject from the study.

#### Definition of Overall Response Using irRC

Overall response using irRC will be based on these criteria (see Table 9):

- **Immune-Related Complete Response (irCR):** Complete disappearance of *all* tumor lesions (index and nonindex together with no new measurable/unmeasurable lesions) for at least 4 weeks from the date of documentation of complete response.
- **Immune-Related Partial Response (irPR):** The sum of the products of the two largest perpendicular diameters of all index lesions is measured and captured as the SPD baseline. At each subsequent tumor assessment, the sum of the products of the two largest perpendicular diameters of all index lesions and of new measurable lesions are added together to provide the Immune Response Sum of Product Diameters (irSPD). A decrease, relative to baseline of the irSPD compared to the previous SPD baseline, of 50% or greater is considered an immune Partial Response (irPR).
- **Immune-Related Stable Disease (irSD):** irSD is defined as the failure to meet criteria for immune complete response or immune partial response, in the absence of progressive disease.
- **Immune-Related Progressive Disease (irPD):** It is recommended in difficult cases to confirm PD by serial imaging. Any of the following will constitute progressive disease:

- At least 25% increase in the sum of the products of all index lesions over nadir SPD calculated for the index lesions.
- At least a 25% increase in the sum of the products of all index lesions and new measurable lesions (irSPD) over the baseline SPD calculated for the index lesions.

### Immune-Related Best Overall Response Using irRC (irBOR)

irBOR is the best confirmed irRC overall response over the study as a whole, recorded between the date of first dose until the last tumor assessment before subsequent therapy (except for local palliative radiotherapy for painful bone lesions) for the individual subject in the study. For the assessment of irBOR, all available assessments per subject are considered.

irCR or irPR determinations included in the irBOR assessment must be confirmed by a second (confirmatory) evaluation meeting the criteria for response and performed no less than 4 weeks after the criteria for response are first met

**Table 9: Derivation of irRC overall responses**

Measurable response	Nonmeasurable response		Overall response
Index and new, measurable lesions (tumor burden),*%	Non-index lesions	New, nonmeasurable lesions	Using irRC
↓100	Absent	Absent	irCR <sup>†</sup>
↓100	Stable	Any	irPR <sup>†</sup>
↓100	Unequivocal progression	Any	irPR <sup>†</sup>
↓≥50	Absent/Stable	Any	irPR <sup>†</sup>
↓≥50	Unequivocal progression	Any	irPR <sup>†</sup>
↓<50 to <25↑	Absent/Stable	Any	irSD
↓<50 to <25↑	Unequivocal progression	Any	irSD
≥25	Any	Any	irPD <sup>†</sup>

\*Decreases assessed relative to baseline (scan prior to start of any protocol therapy), including measurable lesions only

<sup>†</sup>Assuming response (irCR) and progression (irPD) are confirmed by a second, consecutive assessment at least 4 wk apart.

## **8.2. Definitions Associated with Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1**

### **8.2.1. Measurable disease**

The presence of at least one measurable lesion. If the measurable disease is restricted to a solitary lesion, its neoplastic nature should be confirmed by cytology/histology.

### **8.2.2. Measurable lesions**

Measurable lesions are defined as those that can be accurately measured in at least one dimension (longest diameter to be recorded) as ≥20 mm by chest x-ray, as ≥10 mm with CT scan, or ≥10 mm with calipers by clinical exam. All tumor measurements must be recorded in millimeters (or decimal fractions of centimeters).

### 8.2.3. Non-measurable lesions

All other lesions (or sites of disease), including small lesions (longest diameter <10 mm or pathological lymph nodes with  $\geq 10$  to <15 mm short axis), are considered non-measurable disease. Bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis/pulmonitis, inflammatory breast disease, and abdominal masses (not followed by CT or MRI), are considered as non-measurable.

**NOTE:** Cystic lesions that meet the criteria for radiographically defined simple cysts should not be considered as malignant lesions (neither measurable nor non-measurable) since they are, by definition, simple cysts.

‘Cystic lesions’ thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurability described above. However, if non-cystic lesions are present in the same subject, these are preferred for selection as target lesions.

### 8.2.4. Malignant lymph nodes

To be considered pathologically enlarged and measurable, a lymph node must be  $\geq 15$  mm in short axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm). At baseline and in follow-up, only the short axis will be measured and followed.

### 8.2.5. Baseline documentation of “Target” and “Non-Target” lesions Target lesions.

All measurable lesions up to a maximum of 2 lesions per organ and 5 lesions in total, representative of all involved organs, should be identified as **target lesions** and recorded and measured at baseline. Target lesions should be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organs, but in addition should be those that lend themselves to reproducible repeated measurements. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement in which circumstance the next largest lesion which can be measured reproducibly should be selected. A sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the baseline sum diameters. If lymph nodes are to be included in the sum, then only the short axis is added into the sum. The baseline sum diameters will be used as reference to further characterize any objective tumor regression in the measurable dimension of the disease.

### Non-target lesions.

All other lesions (or sites of disease) including any measurable lesions over and above the 5 target lesions should be identified as **non-target lesions** and should also be recorded at baseline. Measurements of these lesions are not required, but the presence, absence, or in rare cases unequivocal progression of each should be noted throughout follow-up.

### 8.2.6. Response Criteria

Evaluation of target lesions

Complete Response (CR)	Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-
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	target) must have reduction in short axis to <10 mm.
Partial Response (PR)	At least a 30% decrease in the sum of the diameters of target lesions, taking as reference the baseline sum diameters
Progressive Disease (PD)	At least a 20% increase in the sum of the diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. (Note: the appearance of one or more new lesions is also considered progressions).
Stable Disease (SD)	Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study

### Evaluation of non-target lesions

Complete Response (CR)	Disappearance of all non-target lesions and normalization of tumor marker level. All lymph nodes must be non-pathological in size (<10 mm short axis)  Note: If tumor markers are initially above the upper normal limit, they must normalize for a subject to be considered in complete clinical response.
Non-CR/ Non-PD	Persistence of one or more non-target lesion(s) and/or maintenance of tumor marker level above the normal limits
Progressive Disease (PD)	Appearance of one or more new lesions and/or unequivocal progression of existing non-target lesions. Unequivocal progression should not normally trump target lesion status. It must be representative of overall disease status change, not a single lesion increase.

\* Although a clear progression of “non-target” lesions only is exceptional, the opinion of the treating physician should prevail.

### Evaluation of best overall response

The best overall response is the best response recorded from the start of the treatment until disease progression/recurrence (taking as reference for PD the smallest measurements recorded since the treatment started). In general, the subject's best response assignment will depend on the achievement of both measurement and confirmation criteria.

**Table 3: Response Assignment**

Target Lesions	Non-Target lesion	New Lesion	Overall response
CR	CR	No	CR
CR	Non-CR/ Non-PD	No	PR
	Not evaluated	No	PR
PR	Non-CR/ Non-PD/ not evaluated	No	PR
SD	Non-CR/ Non-PD/ not evaluated	No	SD
PD	Any	Yes or No	PD
Any	PD*	Yes or No	PD
Any	Any	Yes	PD

\*In exceptional circumstances, unequivocal progression in non-target lesions may be accepted as disease progression.

Subjects with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be classified as having “symptomatic deterioration.” Every effort should be made to document the objective progression even after discontinuation of treatment.

In some circumstances, it may be difficult to distinguish residual disease from normal tissue. When the evaluation of complete response depends on this determination, it is recommended that the residual lesion be investigated (fine needle aspirate/biopsy) to confirm the complete response status.

### **8.2.7. Definitions for Response Evaluation –RECIST version 1.1**

#### **8.2.7.1. First Documentation of Response**

The time between initiation of therapy and first documentation of PR or CR.

#### **8.2.7.2. Duration of Response**

Duration of overall response—the period measured from the time that measurement criteria are met for complete or partial response (whichever status is recorded first) until the date that recurrent or progressive disease is objectively documented, taking as reference for progressive disease the smallest measurements recorded since treatment started.

#### **8.2.7.3. Duration of Overall Complete Response**

The period measured from the time that measurement criteria are met for complete response until the first date that progressive disease is objectively documented.

#### **8.2.7.4. Objective response rate**

The objective response rate is the proportion of all subjects with confirmed PR or CR according to RECIST v1.1, from the start of treatment until disease progression/recurrence (taking as reference for progressive disease the smallest measurements recorded since the start of treatment).

#### **8.2.7.5. Progression Free Survival**

A measurement from the start of the treatment until the criteria for disease progression is met as defined by RECIST 1.1 or death occurs, taking as reference the smallest measurements recorded since the treatment started.

Progression free survival will be measured from the date of initial treatment to the earliest date of disease progression, resection of measurable tumor or death for subjects who fail; and to the date of last contact for subjects who remain at risk for failure.

### **9. BIOLOGICAL SPECIMEN PARAMETERS FOR CORRELATIVES**

Optional submission of unstained slides from an archived tumor block for PD-L1 analysis.

Unstained slides submitted for PD-L1 staining must be cut and sent within 7 days of analysis. A fresh biopsy is NOT mandatory to participate in this trial. Any slides that remain after the initial testing is complete will be stored for possible future studies with consent of subject.

Fine needle aspiration or needle core biopsies that are formalin-fixed and paraffin-embedded are acceptable. A frozen sample, plastic embedded sample, cell block, clot, bone, bone marrow or cytologic specimen are not acceptable for PD-L1 analysis.

Please refer to the Study Procedures Manual for processing, labeling and shipping instructions.

### **10. STUDY DRUG INFORMATION**

#### **10.1. Pembrolizumab**

Please see Investigator's Brochure for detailed information regarding Pembrolizumab

##### **10.1.1 Chemical name and properties**

Humanized X PD-1 \_mAb (H409A11) IgG4

##### **10.1.2 Availability**

Pembrolizumab is an investigational drug and not available outside of a clinical trial.

The site investigator shall take responsibility for and shall take all steps to maintain appropriate records and ensure appropriate supply, storage, handling, distribution and usage of investigational product in accordance with the protocol and any applicable laws and regulations.

##### **10.1.3 Product Descriptions**

Clinical Supplies will be provided by Merck as summarized below:

<b>Product Name &amp; Potency</b>	<b>Dosage Form</b>
Pembrolizumab 100 mg/4mL	Solution for Injection

##### **10.1.4 Packaging and Labeling Information**

Clinical supplies will be affixed with a clinical label in accordance with regulatory requirements.



### **10.1.5 Clinical Supplies Disclosures**

Clinical supplies must be stored in a secure, limited-access location under the storage conditions specified on the label.

Receipt and dispensing of trial medication must be recorded by an authorized person at the trial site.

Clinical supplies may not be used for any purpose other than that stated in the protocol.

### **10.1.6 Adverse Events**

Please see Investigator's Brochure for complete details regarding adverse events related to Pembrolizumab

Pembrolizumab is generally well tolerated immunomodulatory agent and demonstrates a favorable safety profile in comparison to chemotherapy. Important identified risks for pembrolizumab are of an immune mediate nature, including: pneumonitis, colitis, thyroid disorders (hypothyroidism/hyperthyroidism), hepatitis, hypophysitis, Type I diabetes mellitis, uveitis, and nephritis. After a recent review of data, events newly characterized as identified risks also include pancreatitis, myositis, and severe skin reaction; these are included in the reference safety information in the current IB. The majority of events were mild to moderate in severity, were manageable with appropriate care, and rarely required discontinuation of therapy. In addition to the previously noted identified risks, infusion-related reactions are a risk but are not considered immune mediated; these are also further described in the current IB.

## **11. ADVERSE EVENTS**

### **11.1 Definitions of AEs**

#### **11.1.1 Adverse Event**

Adverse event (AE) means any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related. An adverse event (also referred to as an adverse experience) can be any unfavorable and unintended sign (e.g., an abnormal laboratory finding), symptom, or disease temporally associated with the use of a drug, and does not imply any judgment about causality. An adverse event can arise with any use of the drug (e.g., off-label use, use in combination with another drug) and with any route of administration, formulation, or dose, including

A site investigator who is a qualified physician will evaluate all adverse events according to the NCI Common Terminology for Adverse Events (CTCAE), v4. Any adverse event which changes CTCAE grade over the course of a given episode will have each change of grade recorded on the adverse event case report forms/worksheets.

#### **11.1.2 Suspected Adverse Reaction**

Suspected adverse reaction means any adverse event for which there is a reasonable possibility that the drug caused the adverse event. For the purposes of IND safety reporting, 'reasonable possibility' means there is evidence to suggest a causal relationship between the drug and the

adverse event. A suspected adverse reaction implies a lesser degree of certainty about causality than adverse reaction, which means any adverse event caused by a drug.

### 11.1.3 Adverse Reaction

An adverse reaction means any adverse event caused by a drug. Adverse reactions are a subset of all suspected adverse reactions where there is reason to conclude that the drug caused the event.

### 11.1.4 Unexpected Adverse Event

For this study, an AE is considered unexpected when it varies in nature, intensity or frequency from information provided in the current AE list, the IB, the package insert or when it is not included in the informed consent document as a potential risk.

### 11.1.5 Serious Adverse Event

A serious adverse event is any adverse event that:

- Results in death; **NOTE:** Death due to progressive disease is not considered a SAE unless the event was related to the study drug.
- Is life-threatening (defined as an event in which the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe)
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly or birth defect
- Is an important medical event (defined as a medical event(s) that may not be immediately life-threatening or result in death or hospitalization but, based upon appropriate medical and scientific judgment, may jeopardize the subject or may require intervention (e.g., medical, surgical) to prevent one of the other serious outcomes listed in the definition above). Examples of such events include, but are not limited to:
  - Intensive treatment in an emergency room or at home for allergic bronchospasm
  - Blood dyscrasias or convulsions not resulting in hospitalization
  - An overdose (whether accidental or intentional). Any adverse event associated with an overdose is considered a serious adverse event. An overdose that is not associated with an adverse event is considered a non-serious event of clinical interest. Both cases must be immediately reported. See section 11.3.

### 11.1.6 Events of Clinical Interest

Selected non-serious and serious adverse events are also known as Events of Clinical Interest (ECI). ECIs must be reported from the date of first dose through 90 days following cessation of treatment, or 30 days after the initiation of a new anticancer therapy, whichever is earlier. ECIs will be reported by sites **within one business day** to HCRN. HCRN will report all ECIs to Merck Global Safety (Attn: Worldwide Product Safety; FAX 215-993-1220 **within one business day** of becoming aware of event).

#### Events of clinical interest for this trial include:

1. An overdose of Merck product, as defined in Section 11.3 that is not associated with clinical symptoms or abnormal laboratory results.

2. An elevated AST or ALT lab value that is greater than or equal to 3X the upper limit of normal and an elevated total bilirubin lab value that is greater than or equal to 2X the upper limit of normal and, at the same time, an alkaline phosphatase lab value that is less than 2X the upper limit of normal, as determined by way of protocol-specified laboratory testing or unscheduled laboratory testing.\*

**NOTE:** These criteria are based upon available regulatory guidance documents. The purpose of the criteria is to specify a threshold of abnormal hepatic tests that may require an additional evaluation for an underlying etiology.

3. In the event a subject develops any of the following AEs, a detailed narrative of the event should be reported as an ECI to the HCRN **within one business day** and HCRN will report it to Merck Global Safety **within one business day** of the event: (Attn: Worldwide Product Safety; FAX 215 993-1220)).

Subjects should be assessed for possible ECIs prior to each dose. Lab results should be evaluated and subjects should be asked for signs and symptoms. Subjects who develop an ECI thought to be immune-related should have additional testing to rule out other etiologic causes. If lab results or symptoms indicate a possible immune-related ECI, then additional testing should be performed to rule out other etiologic causes. If no other cause is found, then it is assumed to be immune-related.

## **11.2 Adverse Event Reporting**

### **11.2.1 Site Requirements for Recording Adverse Events**

Adverse events (AEs) will be recorded from the time of consent and for at least 30 days after treatment discontinuation, regardless of whether or not the event(s) are considered related to trial medications. All AEs considered related to trial medication will be followed until resolution, return to baseline, or deemed clinically insignificant, even if this occurs post-trial.

Adverse events will not be collected for subjects during the pre-screening period (for determination of archival tissue status) as long as that subject has not undergone any protocol-specified procedure or intervention. If the subject requires a blood draw, fresh tumor biopsy etc., the subject is first required to provide consent to the main study and AEs will be captured according to guidelines for standard AE reporting.

### **11.2.2 SAE Reporting from Site to HCRN**

Site investigators will report to HCRN any SAE, or follow up to a SAE, including death due to any cause other than progression of the cancer under study, that occurs to any subject from the time the consent is signed through 90 days following the last dose of study drug, or the initiation of new anti-cancer therapy, whichever is earlier, whether or not related to Merck product.

Progression of the cancer under study is not considered an adverse event unless it is considered to be drug related by the investigator.

All AEs and SAEs will be recorded in the subject's medical record and on the appropriate study specific eCRF form within the EDC system. In addition, all SAEs will be reported on the SAE Submission Form and submitted to HCRN per guidelines outlined in this section.

Site investigators and other site personnel must report any SAEs occurring during the course of the study to HCRN **within one business day** of discovery of the event. This includes events both related and unrelated to the investigational product.

The definition of "related" being that there is a reasonable possibility the drug caused the adverse experience.

<b>Unrelated</b>	The Adverse Event is <i>clearly not related</i> to the investigational agent(s)
<b>Unlikely</b>	The Adverse Event is <i>doubtfully related</i> to the investigational agent(s)
<b>Possible</b>	The Adverse Event <i>may be related</i> to the investigational agent(s)
<b>Probable</b>	The Adverse Event is <i>likely related</i> to the investigational agent(s)
<b>Definite</b>	The Adverse Event is <i>clearly related</i> to the investigational agent(s)

The completed SAE Submission Form (see SPM) must be sent either electronically to [SAFETY@hoosiercancer.org](mailto:SAFETY@hoosiercancer.org) or by fax to (317-921-2053) to Hoosier Cancer Research Network. The site investigator is responsible for informing the IRB and/or the Regulatory Authority of the SAE as per local requirements.

The original copy of the SAE Submission Form and the e-mail correspondence or the fax confirmation sheet must be kept within the study file at the study site.

Follow-up information will be sent electronically [or by](#) fax to the Hoosier Cancer Research Network, using a new SAE Submission Form. Each re-occurrence, complication, or progression of the original event should be reported as a follow-up to that event regardless of when it occurs.

### 11.2.3 HCRN Requirements for Reporting SAEs to Merck

HCRN will report any SAE from the time the consent is signed through 90 days following the last dose of study drug, or the initiation of new anti-cancer therapy, whichever is earlier, whether or not related to Merck product. The report will be sent to Merck **within one business day** of receipt of the SAE Submission Form. Hoosier Cancer Research Network will fax follow up information as reasonably requested to Merck.

SAE reports and any other relevant safety information are to be forwarded to the Merck Global Safety facsimile number: +1-215-993-1220.

### 11.2.4 Sponsor-Investigator Responsibilities

HCRN will send a SAE summary to the sponsor-investigator within 1 business day of receipt of SAE Submission Form from a site. The sponsor-investigator will promptly review the SAE summary and assess for expectedness and relatedness.

#### **11.2.5 HCRN Requirements for Reporting to FDA**

HCRN will manage the Investigational New Drug Application (IND) associated with this protocol on behalf of the sponsor-investigator. HCRN will cross-reference this submission to the Merck's parent IND at the time of submission. Additionally, HCRN will submit a copy of these documents to Merck at the time of submission to FDA.

For protocols conducted under an IND, HCRN will be responsible for all communication with the FDA in accordance with 21CFR312 including but not limited to the 7 and 15 Day Reports, as well as an Annual Progress Report. Additionally HCRN will submit a copy of these reports to Merck at the time of submission to FDA.

#### **11.2.6 IND Safety Reports Unrelated to this Trial**

Merck will provide to HCRN IND safety reports from external studies that involve the study drug(s) per their guidelines. HCRN will forward safety reports to the sponsor-investigator who will review these reports and determine if revisions are needed to the protocol or consent. HCRN will forward these reports to participating sites **within 1 business day** of receiving the sponsor-investigator's review. Based on the sponsor-investigator's review, applicable changes will be made to the protocol and informed consent document (if required). All IND safety reports will also be made available to sites via OnCore®.

Upon receipt from HCRN, site investigators (or designees) are responsible for submitting these safety reports to their respective IRBs, as per their IRB policies.

#### **11.2.7 Definition of an Overdose for This Protocol and Reporting of Overdose to HCRN and Merck**

For purposes of this trial, an overdose will be defined as any dose of 1,000 mg or greater ( $\geq 5$  times the indicated dose). No specific information is available on the treatment of overdose of pembrolizumab. In the event of overdose, pembrolizumab should be discontinued and the subject should be observed closely for signs of toxicity. Appropriate supportive treatment should be provided if clinically indicated.

If an adverse event(s) is associated with ("results from") the overdose of a Merck product, the adverse event(s) is reported as a serious adverse event, even if no other seriousness criteria are met.

If a dose of Merck's product meeting the protocol definition of overdose is taken without any associated clinical symptoms or abnormal laboratory results, the overdose is reported as a non-serious Event of Clinical Interest (ECI), using the terminology "accidental or intentional overdose without adverse effect."

All reports of overdose with and without an adverse event must be reported to HCRN **within one business day** (HCRN will report to Merck Global Safety **within one business day** of the event). (Attn: Worldwide Product Safety; FAX 215 993-1220).

#### **11.4 Reporting of Pregnancy and Lactation to HCRN and to Merck**

Although pregnancy and lactation are not considered adverse events, it is the responsibility of site investigators or their designees to report any pregnancy or lactation in a subject (spontaneously reported to them), including the pregnancy of a male subject's female partner that occurs during the trial or within 120 days of completing the trial, or 30 days following cessation of treatment if the subject initiates new anticancer therapy, whichever is earlier. All subjects and female partners of male subjects who become pregnant must be followed to the completion/termination of the pregnancy. Pregnancy outcomes of spontaneous abortion, missed abortion, benign hydatidiform mole, blighted ovum, fetal death, intrauterine death, miscarriage and stillbirth must be reported as serious events (Important Medical Events). If the pregnancy continues to term, the outcome (health of infant) must also be reported.

Such events must be reported to HCRN **within one business day** on the SAE Submission Form (see SPM). (HCRN will report to Merck Global Safety **within one business day** of the event). (Attn: Worldwide Product Safety; FAX 215 993-1220).

### **12. STATISTICAL CONSIDERATIONS**

#### **12.1. General Considerations**

Statistical analysis will be the responsibility of the Department of Biostatistics at Indiana University School of Medicine (IUSM) & School of Public Health (SPH). Summary statistics will be generated for both continuous and categorical variables. Missing data will not be imputed. Changes from the analysis plan will not require an amendment to the protocol unless it changes a significant feature in the protocol.

#### **12.2. Study Design**

This is an open label, multi-institutional, single arm phase II trial. No randomization or blinding will be involved.

#### **12.3. Criteria for Stopping Study**

After the first 10 subjects are treated with at least one dose of study drug and observed for a minimum of 3 months after first dose of study therapy, further accrual will be halted to evaluate “unacceptable toxicities warranting early closure of the trial” defined as a) any definitive pembrolizumab-related death; or b) any unexpected and previously unreported grade 4 toxicities definitely related to pembrolizumab. If such events are observed in one subject, the DMSB will discuss and decide whether to recommend termination of the trial. If such events are observed in two or more subjects, the trial will be terminated.

Pembrolizumab-related death will be continuously monitored through the trial. Whenever the first case happens, the DMSB will meet and discuss whether to recommend stoppage of the trial. Whenever there are two cases in cumulative, the trial will be terminated.

Pneumonitis of grade 3 and 4 will be continuously monitored starting from N=10. An overall rate of 20% or above is considered as unacceptable. If the probability of the grade 3/4 pneumonitis rate being less than 20% drops below 0.1, the trial will be terminated. A priori, the rate is assumed to follow  $\theta \sim \text{beta}(1,1)$ . Conditional on observing  $y$  events out of  $n$  subjects, the

rate follows  $\theta|y, n \sim \text{beta}(1 + y, 1 + n - y)$ . The probability of  $\theta < 20\%$  is  $\int_0^{0.2} f(\theta|n, y) d\theta$ . The threshold is defined as the smallest  $y$  corresponding to the integral being smaller than 0.1, which will lead to termination of the trial.

**Table 10: Thresholds “k” for N=10 to N=93**

N	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24
k	4	4	4	5	5	5	6	6	6	6	7	7	7	7	8
N	25	26	27	28	29	30	31	32	33	34	35	36	37	38	39
k	8	8	8	9	9	9	9	10	10	10	10	11	11	11	11
N	40	41	42	43	44	45	46	47	48	49	50	51	52	53	54
k	12	12	12	12	12	13	13	13	13	14	14	14	14	15	15
N	55	56	57	58	59	60	61	62	63	64	65	66	67	68	69
k	15	15	16	16	16	16	16	17	17	17	17	18	18	18	18
N	70	71	72	73	74	75	76	77	78	79	80	81	82	83	84
k	19	19	19	19	19	20	20	20	20	21	21	21	21	22	22
N	85	86	87	88	89	90	91	92	93						
k	22	22	22	23	23	23	23	24	24						

## 12.4. Analysis Datasets

The definitions of the study populations are listed below.

Population	Definition
Enrolled	This will comprise all subjects who meet the eligibility criteria and are registered onto the study.
Evaluable for Primary Objective	This will comprise all subjects who receive at least one dose of trial drug and either undergo at least one post-baseline assessment
Evaluable for Secondary objectives	This will comprise all subjects who receive at least one dose of trial drug and either undergo at least one post-baseline assessment or die before any evaluation.
Evaluable for Safety	This will comprise all subjects who receive at least one dose of trial drug
Intention-to-treat (ITT)	This will comprise all subjects who meet the eligibility criteria and are registered onto the study irrespective of their compliance to the planned course of treatment.
Treated	This will comprise all subjects who have been exposed to the planned course of treatment to any extent.

## 12.5. Sample Size, Accrual, Study Duration and Replacement Rules

Efficacy of pembrolizumab will be quantified and evaluated by the time to death or distant metastasis, depending on which occurs first. Under the conventional chemoradiation, the median time is around 12-months. This estimate is generated based upon the previous trial by the Hoosier Oncology Group (LUN 01-24) [35, 36]. In this trial, subjects were randomized to observation vs. docetaxel if they had completed chemoradiation, had non-progressive disease, good performance status and end organ function. The median time to progression (mostly with distant mets) was 12 months in the observation arm. This group of subjects will most closely resemble the subject population enrolled onto this trial. We expect pembrolizumab to improve the median time by 50%. Brookmeyer and Crowley’s method will be used to test the following

one-sided hypotheses:  $H_0: m \leq 12\text{-month}$  versus  $H_a: m > 12\text{-month}$ . The accrual period is expected to be 24-months, following by an additional 12-months follow-up. Thus, the overall study duration will be 36 months. With type I error level as 0.05,  $N=83$  subjects are required to obtain a power level of 0.80. The sample size is further adjusted to  $N = 93$  to account for 10% lost-to-follow-up. If an ineligible subject is accidentally enrolled, that subject will be removed and replaced with an eligible subject.

#### **12.6. Subject Demographics/Other Baseline Characteristics**

Demographic and other baseline data will be summarized descriptively for all subjects in the ITT set.

#### **12.7. Concomitant Medications**

Concomitant medications and significant non-drug therapies prior and after the start of the study drug will be summarized for the treated set.

#### **12.8. Primary Objective**

The primary objective is to evaluate the time to death or distant metastasis (TTD), depending on which occurs first. The enrolled set will be used for the primary analysis.

Kaplan-Meier method will be used for estimation. Brookmeyer and Crowley's method will be used to calculate the 95% confidence interval of the median time and to test the following one-sided hypotheses:  $H_0: m \leq 12\text{-month}$  versus  $H_a: m > 12\text{-month}$ .  $P\text{-value} < 0.05$  will be considered as significant.

#### **12.9. Secondary Objectives**

Key secondary objectives are progression free survival (PFS), overall survival (OS) and toxicities of pembrolizumab TTD in evaluable set is also a secondary objective.

PFS and OS will be estimated by Kaplan-Meier method. They will be analyzed for both the enrolled set and the evaluable set. TTD will be estimated by Kaplan-Meier method for the evaluable set.

Toxicities will be presented as rates and 95% Agresti-Coull confidence intervals. The treated set will be used for toxicity analysis.

#### **12.10. Safety Analysis**

The Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 and the Merck criteria for immunological side effects will be used jointly to report toxicities.

Safety analyses will be performed for the treated set. Toxicities will be summarized by grade level, with and without considering relevance to treatment.

#### **12.11. Exploratory Objectives**

Exploratory analysis is planned to characterize the rate of expression PD-L1 in stage III NSCLC, and correlate with histology, PFS, OS and toxicity.



Rates and 95% confidence intervals will be generated for PD-L1 expressions. Their associations with TTD, PFS and OS will be evaluated by Cox proportional hazard models.

#### **12.12. Subgroup Analysis**

Both efficacy and toxicity outcomes will be evaluated in subgroup analysis based on PD-L1 expressions, as well for subjects that have had up to 2 cycles of consolidation therapy. Additional subgroup analyses will be performed for toxicities based on primary treatment as chemotherapy or radiation therapy, and the dosage of radiations.

### **13. TRIAL MANAGEMENT**

#### **13.1 Data and Safety Monitoring Plan**

This study will be conducted in accordance with the IU Simon Cancer Center's (IUSCC) Data and Safety Monitoring Plan. Study monitoring will include a risk-based monitoring strategy as defined in the Data Management Plan associated with this protocol. This study will have a Data Safety Monitoring Board as described below and a DSMB Charter.

In addition HCRN data and safety monitoring activities include:

- Conduct review of clinical trial for progress and safety
- Review of all adverse events requiring expedited reporting as defined in the protocol
- Provide sponsor-investigator with trial progress and safety information as required.
- Notification of participating sites of adverse events requiring expedited reporting and subsequent committee recommendations for study modifications

#### **13.2 Data and Safety Monitoring Board**

This study will have a Data and Safety Monitoring Board (DSMB) that will review and monitor study progress, toxicity, safety and other data from this trial. The DSMB is separate from the IU Simon Cancer Center (IUSCC) Data and Safety Monitoring Committee (DSMC). The board is chaired by an independent medical oncologist external to this trial. Questions about subject safety or protocol performance will be addressed with the sponsor-investigator, statistician and study team members. Should any major concerns arise; the DSMB will offer recommendations regarding whether or not to suspend the trial.

The DSMB will meet after the first 10 subjects are treated with at least one dose of study drug and observed for a minimum of 3 months after first dose of study therapy, then twice a year thereafter to review accrual, toxicity, response and reporting information. Information to be provided to the DSMB may include: subject accrual, treatment regimen information, adverse events and serious adverse events reported by category, summary of any deaths on study, audit and/or monitoring results.

The DSMB will provide a recommendation to the team after all information is reviewed. This information will also be provided to the site investigator sites for submission to the respective IRB according to the local IRB's policies and procedures.

### **14. DATA HANDLING AND RECORD KEEPING**

#### **14.1 Case Report Forms and Submission**

This study will utilize electronic case report form (eCRF) in the Hoosier Cancer Research Network (HCRN) electronic data capture (EDC) system. The EDC system is a comprehensive database used by HCRN and properly used is compliant with Title 21 CFR Part 11. Access to the data through EDC system is restricted by user accounts and assigned roles. Once logged into the EDC system with a user ID and password, the EDC system defines roles for each user, which limits access to appropriate data. User information and passwords can be obtained by contacting HCRN at (317) 921-2050.

Generally, clinical data will be electronically captured in the EDC system and correlative results will be captured in the EDC system or other secure database. If procedures on the study calendar are performed for standard of care, at minimum, that data will be captured in the source document. Select standard of care data will also be captured in the EDC system, according to study-specific objectives. Please see the SPM guidelines for further details.

The completed dataset is the sole property of the sponsor-investigator's institution. It should not be made available in any form to third parties, except for authorized representatives of appropriate Health/Regulatory Authorities, without written permission from the sponsor-investigator and HCRN.

#### **14.2 Record Retention**

To enable evaluations and/or audits from Health Authorities/HCRN, the site investigator agrees to keep records, including the identity of all participating subjects (sufficient information to link records; e.g., hospital records), all original signed informed consent forms, copies of all source documents, and detailed records of drug disposition. To comply with international regulations, the records should be retained by the site investigator in compliance with regulations.

During data entry, range and missing data checks will be performed on-line. The checks to be performed will be documented in the Data Monitoring Plan for the study. A summary report (QC Report) of these checks together with any queries resulting from manual review of the eCRF's will be generated for each site and transmitted to the site and the site monitor. Corrections will be made by the study site personnel. This will be done on an ongoing basis.

#### **14.3 Confidentiality**

There is a slight risk of loss of confidentiality of subject information. All records identifying the subject will be kept confidential and, to the extent permitted by the applicable laws and/or regulations, will not be made publicly available.

Information collected will be maintained on secure, password protected electronic systems. Paper files that contain personal information will be kept in locked and secure locations only accessible to the study team. Samples that are collected will be identified by a subject study number assigned at the time of registration to the trial. Any material issued to collaborating researchers will be anonymized and only identified by the subject study number. Subjects will be informed in writing that some organizations including the sponsor-investigator and his/her research associates, HCRN, Merck, IRB, or government agencies, like the FDA, may inspect their medical records to verify the information collected, and that all personal

information made available for inspection will be handled in strictest confidence and in accordance with local data protection laws.

If the results of the study are published, the subject's identity will remain confidential.

#### **14.4 Changes to the Protocol**

Study procedures will not be changed without the mutual agreement of the sponsor-investigator, Hoosier Cancer Research Network, and Merck.

If it is necessary for the study protocol to be amended, the amendment or a new version of the study protocol (amended protocol) will be generated by the Hoosier Cancer Research Network and must be approved by each IRB, Merck, and if applicable, also the local regulatory authority. Local requirements must be followed.

If a protocol amendment requires a change to the Written Informed Consent Form, then the IRB must be notified. Approval of the revised Written Informed Consent Form by the IRB is required before the revised form is used.

The site investigator is responsible for the distribution of these documents to his or her IRB, and to the staff at his or her center. The distribution of these documents to the regulatory authority will be handled according to local practice.

Merck's willingness to supply study drug is predicated upon the review of the protocol. The Hoosier Cancer Research Network agrees to provide written notice to Merck of any modifications to the protocol or informed consent.

### **15. ETHICS**

#### **15.1 Ethics Review**

The final study protocol, including the final version of the Written Informed Consent Form, must be approved in writing by an IRB. The site investigator must submit written approval to the HCRN office before he or she can enroll any subject into the study.

The site investigator is responsible for informing the IRB of any amendment to the protocol in accordance with local requirements. In addition, the IRB must approve all advertising used to recruit subjects for the study. The protocol must be re-approved by the IRB annually, as local regulations require.

Progress reports and notifications of serious unexpected adverse drug reactions will be provided to the IRB according to local regulations and guidelines.

The site investigator is also responsible for providing the IRB with reports of any serious adverse drug reactions from any other study conducted with the investigational product. Merck will provide this information to HCRN. These reports will be reviewed by the sponsor-investigator and those considered unexpected and possibly related to protocol therapy plus all deaths within 90 days of discontinuing treatment will be forwarded to participating sites for submission to their

Institutional Review Boards per their guidelines. All other events will be held and submitted to the sites for continuing review.

### **15.2 Ethical Conduct of the Study**

The study will be performed in accordance with ethical principles originating from the Declaration of Helsinki, which are consistent with ICH/Good Clinical Practice, and applicable regulatory requirements.

### **15.3 Informed Consent Process**

The site investigator will ensure the subject is given full and adequate oral and written information about the nature, purpose, possible risks and benefits of the study. Subjects must also be notified they are free to discontinue from the study at any time. The subject should be given the opportunity to ask questions and allowed time to consider the information provided. The subject's signed and dated informed consent must be obtained before conducting any procedure specifically for the study. The site investigator must store the original, signed Written Informed Consent Form. A copy of the signed Written Informed Consent Form must be given to the subject.

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